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(PCT Rule 61.2)

To:

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Applicant LEWIS, Jerry et al	

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(54) Title: MICROCRYSTALLINE SUGARS OR SUGAR-ALCOHOLS; METHOD FOR PREPARING THE SAME

(54) Titre: SUCRES OU ALCOOLS DE SUCRES MICROCRISTALLINS; PROCEDE POUR LES PREPARER

(57) Abstract

A composition containing sugar microcrystals is disclosed. Essentially, the crystals are uniform unbroken single crystals with a regular geometrical shape and a grain size following a Gaussian distribution of which the median is of around 20-220 μm, while the coefficient of variation is of around 20-50 %, particularly 30-45 %, 35-45 % or 30-40 %. The term "sugar" designates mono-, di- and oligosaccharides, as well as the polyols obtained by their reduction.

(57) Abrégé

L'invention a pour objet une composition contenant des microcristaux de sucre caractérisée en ce que les cristaux sont essentiellement des monocristaux de forme géométrique régulière, ne présentant par de brisure, homogènes les uns par rapport aux autres, et en ce que la granulométrie suit une distribution gaussienne dont la médiane est d'environ 20 μm à environ 220 μm, le coefficient de variation étant d'environ 20 % à environ 50 %, notamment d'environ 30 % à 45 %, ou d'environ 35 % à 45 %, ou d'environ 30 % à 40 %. Par "sucre", on désigne les mono-, di- et oligosaccharides, ainsi que les polyols obtenus par réduction de ceux-ci.

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SUCRES OU ALCOOLS DE SUCRES MICROCRISTALLINS; PROCEDE POUR LES PREPARER

L'invention traite de compositions de sucre sous une forme cristalline, fluide et non mottante. La présente invention concerne le domaine de la cristallisation du sucre, et plus précisément, elle décrit une méthode d'obtention de compositions de sucre cristallisé de granulométrie fine. L'invention décrit une composition de sucre cristallin de forme régulière, de granulométrie fine et bien définie.

Pendant la cristallisation, la répartition granulométrique des cristaux dépend principalement des processus suivants :

- la nucléation,
- la croissance des cristaux,
- l'attrition,
- l'agglomération,
- la maturation des cristaux.

Pour obtenir une grande quantité de cristaux réguliers et de granulométrie fine, il est nécessaire d'appliquer un procédé favorisant la nucléation plus que la croissance cristalline. Pour cela il est nécessaire d'utiliser les moyens appropriés permettant un bon contrôle des paramètres de cristallisation.

Les procédés de cristallisation existants ne permettent pas l'obtention directe d'une grande quantité de cristaux de sucre de forme régulière avec une granulométrie très fine. Dans la fabrication de divers types de sucre, un procédé a été développé, plus connu comme étant un procédé de transformation. Ce procédé est utilisé pour la production de sucre en poudre granulé, fluide, non mottant et facilement dispersable en solution aqueuse. Ce procédé a été abondamment décrit dans plusieurs brevets.

US 3,194,682 (Tippens et al.) décrit un procédé utilisant un sirop concentré à 95-97 brix (% en poids de matières sèches) à 121-129°C qui est soumis à un refroidissement rapide sous agitation énergique. Cette méthode permet la fabrication d'agglomérats dont les cristaux de sucre sont de taille fondant (3-50 microns).

US 3,365,331 (Miller et al.) décrit un procédé similaire qui conduit à la fabrication d'agglomérats. Dans ce cas, les cristaux sont obtenus par battage d'un sirop sursaturé.

Dans le brevet EP 0 052 413, le procédé de battage à une température bien contrôlée permet une incorporation de composés thermosensibles dans le produit final.

Tous les procédés décrits conduisent à une poudre de sucre fin granulé. Les granules sont de forme irrégulière donnant des poudres de basse densité. La sélection de la granulométrie se faisant par tamisage, le rendement en une classe de poudre est de ce fait faible. Il existe donc un besoin de développement d'un procédé permettant la fabrication avec de bons rendements de cristaux réguliers et de granulométrie fine, ce que permet la présente invention.

Plus précisément, l'invention a notamment pour objet une composition contenant des microcristaux de sucre caractérisée en ce que les cristaux de sucre obtenus sont de forme régulière, ne s'agglomèrent pas, et leur répartition granulométrique est de type gaussien autour d'une ouverture moyenne comprise entre 20 et 220 μm, notamment 20 et 200 μm, avec un coefficient de variation (CV) compris entre 20% et 50% ou leur répartition granulométrique est caractérisée par un indice d'uniformité compris entre 1 et 5, notamment entre 2.5 et 3.5.

La granulométrie est déterminée par tamisage sur une série de tamis normalisés (NF11-501) de 200 mm de diamètre.

Le coefficient de variation (CV) est calculé par la formule :

$CV = 100 \times \sigma/O.M.$,

dans laquelle σ est l'écart type et O.M. est l'ouverture moyenne.

S'agissant de l'indice d'uniformité, il est obtenu par tamisage de la composition cristalline et calculé suivant la formule :

$$\frac{\text{Taille de particule correspondant à 60\% du passage de la poudre}}{\text{Taille de particule correspondant à 10\% du passage de la poudre}}$$

L'invention a aussi pour objet une méthode d'obtention d'une composition de sucre microcristallin caractérisée en ce que les cristaux ont une granulométrie moyenne comprise entre 20 et 220 μm, notamment 20 et 200 μm obtenus après les étapes suivantes :

a) fabrication d'un sirop concentré,

b) diminution de la pression,

c) évaporation sous pression réduite avec agitation vigoureuse dans la zone de cristallisation jusqu'à l'apparition des cristaux,

d) arrêt de l'évaporation et maintien de l'agitation pendant un certain temps,

e) reprise de l'évaporation et de l'agitation jusqu'à l'obtention d'un produit sec,

la température du sirop étant maintenue de 40°C à 100°C, et notamment de 70°C à 100°C pendant la durée des étapes a) à e) décrites ci-dessus.

Ce procédé sera dans la suite désigné par "procédé I".

Selon un mode de réalisation avantageux, l'invention concerne une composition contenant des microcristaux de sucre caractérisée en ce que les cristaux sont essentiellement des monocristaux de forme géométrique régulière, ne présentant pas de brisure, homogènes les uns par rapport aux autres, et en ce que

- la granulométrie suit une distribution gaussienne dont la médiane est d'environ 20 à environ 220 μm, et notamment d'environ 20 μm à environ 200 μm, le coefficient de variation étant d'environ 20% à environ 50%, notamment d'environ 30% à 45%, ou d'environ 35% à 45%, ou d'environ 30% à 40% ou

- la répartition granulométrique est caractérisée par un indice d'uniformité compris entre 1 et 5, notamment entre 2.5 et 3.5.

Par "sucre", on désigne les mono-, di- et oligosaccharides, ainsi que les polyols obtenus par réduction de ceux-ci.

L'expression "monocristaux ne présentant pas de brisure" signifie que ces cristaux ne présentent pas d'angles aigus liés à une opération de broyage.

L'expression "homogènes les uns par rapport aux autres" signifie que ces cristaux sont de géométrie cristalline comparable.

Avantageusement, les monocristaux des compositions de l'invention ont une ouverture moyenne d'environ 80 μm à environ 120 μm.

La composition de l'invention est caractérisée en ce qu'elle présente les propriétés suivantes :

- sa vitesse de dissolution est d'environ 5 à environ 10, notamment d'environ 7 à environ 9 secondes, dans les conditions suivantes : 10 g de composition pour 100 ml d'eau pure déminéralisée, à la température de 18°C,

- elle est non mottante,

- son indice de coulabilité est supérieur à environ 80, et varie d'environ 80 à environ 85, notamment d'environ 81 à environ 82, mesuré selon le test d'Hosakawa, tel que décrit dans IRON WORKS, LTD, Osaka, Japon, et lorsqu'il s'agit du glucose, l'indice de coulabilité est d'environ 55 à environ 70,

- la densité du produit tassé est d'environ 0,90 à environ 1,00, notamment d'environ 0,97 à environ 1,00, et la densité du produit non tassé est d'environ 0,75 à environ 0,90, notamment d'environ 0,83 à environ 0,87, mesurées selon le test d'Hosakawa, et lorsque le susdit produit est du glucose, la densité du

produit tassé est d'environ 0,70 à environ 0,90 et la densité du produit non tassé est d'environ 0,50 à environ 0,70.

L'expression "non mottante" signifie que les cristaux ne s'agglomèrent pas entre eux dans les conditions normales de température (10 à 30°C) et humidité (40 à 80 %) ambiantes.

Selon un autre mode de réalisation avantageux de l'invention, la composition est caractérisée en ce qu'elle contient des ingrédients additionnels, à raison d'environ 0% à environ 10%, et avantageusement à raison d'environ 5%, ces ingrédients étant de façon avantageuse choisis parmi les composés thermosensibles, des composés ayant des propriétés alimentaires ou pharmacologiques, ou des composés ayant un goût ou une couleur recherchés.

La composition de l'invention est susceptible d'être obtenue par le procédé comprenant les étapes suivantes :

a) on prépare un sirop de saccharose concentré, d'environ 60 à environ 97, notamment 75% en poids de matières sèches,

b) on réduit la pression qui passe de la pression atmosphérique à une valeur d'environ 100 à environ 300 mbars, notamment d'environ 200 mbars, pour commencer à évaporer une partie de l'eau contenue dans le sirop de sucre, le taux d'évaporation étant d'environ 20%,

c) on évapore une partie de l'eau contenue dans le sirop de sucre sous pression réduite (environ 200 mbars) et on brasse le sirop, notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, jusqu'à atteindre un coefficient de sursaturation de sucre compris entre 1 et 1,3, notamment 1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on effectue la suite de la cristallisation par arrêt de l'évaporation et de l'agitation vigoureuse (battage), et maintien d'une agitation régulière (brassage) pendant le temps nécessaire à l'obtention des cristaux de taille souhaitée, et avantageusement pendant environ 5 mn à environ 20 mn,

e) on reprend l'évaporation (toujours avec brassage du milieu à une vitesse d'environ 100 à environ 250 m/mn) jusqu'à l'obtention de cristaux contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant maintenue à une valeur d'environ 70°C à environ 100°C, pendant toute la durée du procédé, et la pression étant avantageusement maintenue à environ 200 mbars pendant les étapes c) à e).

Selon un mode de réalisation avantageux de l'invention, le procédé I est caractérisé par les étapes suivantes :

a) on prépare un sirop de saccharose concentré, d'environ 60 à environ 97, notamment 75% en poids de matières sèches,

b) on réduit la pression qui passe de la pression atmosphérique à une valeur d'environ 100 à environ 300 mbars, notamment d'environ 200 mbars, pour commencer à évaporer une partie de l'eau contenue dans le sirop de sucre, le taux d'évaporation étant d'environ 20%,

c) on évapore une partie de l'eau contenue dans le sirop de sucre sous pression réduite (environ 200 mbars) et on brasse le sirop, notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, jusqu'à atteindre un coefficient de sursaturation de sucre compris entre 1 et 1,3, notamment 1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné, notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on effectue la suite de la cristallisation par arrêt de l'évaporation et de l'agitation vigoureuse (battage), et maintien d'une agitation régulière (brassage) pendant le temps nécessaire à l'obtention des cristaux de taille souhaitée, et avantageusement pendant environ 5 mn à environ 20 mn,

e) on reprend l'évaporation (toujours avec brassage du milieu à une vitesse d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn jusqu'à l'obtention de cristaux contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant maintenue à une valeur d'environ 40°C à environ 100°C, notamment d'environ 70°C à environ 100°C, pendant toute la durée du procédé, et la pression étant avantageusement maintenue à environ 200 mbars pendant les étapes c) à e).

Le procédé de l'invention commence avec la préparation du sirop concentré de sucre. La concentration adaptée est comprise, à titre indicatif, entre 60 et 80% en poids de matières sèches. Afin d'éviter la recristallisation et la dégradation du sucre ou tout autre produit ajouté à la solution, la température est maintenue de 40°C à 100°C, notamment de 70°C à 100°C. La pression est réduite à 100-300 mbars pour démarrer l'évaporation. En même temps, le sirop est maintenu sous agitation. Cette agitation mécanique ou brassage du sirop est nécessaire à l'homogénéisation du milieu, et est réalisée à l'aide d'un mobile d'agitation avantageusement placé en fond de cuve utilisée dans le procédé de l'invention. A titre d'illustration, ce brassage peut être réalisé avec un

mélangeur-évaporateur, un cristalliseur, un mélangeur-homogénéiseur, un mélangeur-malaxeur ou tout autre équipement adapté. Il est important que ce brassage soit énergique et que l'énergie apportée au sirop soit contrôlée. En outre, pour le bon fonctionnement du procédé, l'installation doit pouvoir fonctionner sous pression réduite et température régulée.

L'agitation vigoureuse, avantageusement effectuée par battage par impact, de la solution stimule la formation de germes et un voile est observable après un certain temps. Ces conditions sont maintenues pendant quelques minutes et ensuite, l'évaporation est arrêtée. A titre d'illustration, les essais qui sont décrits dans les exemples de l'invention sont réalisés sur un évaporateur-mélangeur Guédu de 45 litres, équipé pour le battage par impact d'un mixeur ou de couteaux dont la vitesse de rotation est d'environ 1000 à environ 2000 tours/mn.

Le brassage est maintenu afin de mieux contrôler la croissance des cristaux. Pendant la phase finale, l'évaporation est poursuivie avec brassage jusqu'à l'obtention de cristaux secs.

La variation de la vitesse d'agitation pour le brassage du milieu, du taux d'évaporation et de la durée des différentes étapes, permet de préparer des cristaux d'une granulométrie moyenne bien définie pouvant être obtenus de façon reproductible.

La composition de l'invention est également susceptible d'être obtenue par un procédé comprenant les étapes suivantes :

a) on prépare un sirop concentré,

b) on évapore le sirop sous pression avec agitation vigoureuse dans la zone de cristallisation jusqu'à l'apparition des cristaux, avec contrôle de la température et du débit d'évaporation jusqu'à une teneur en matières sèches d'environ 80% à environ 90%,

c) on poursuit l'évaporation avec réduction de la vitesse d'agitation jusqu'à l'obtention d'un produit sec, la température étant maintenue constante par rapport à l'étape précédente,

la température étant ajustée et maintenue à une valeur déterminée dans l'intervalle d'environ 40°C à environ 100°C, et notamment d'environ 70°C à environ 100°C, pendant la durée des étapes a) à c) décrites ci-dessus.

La composition de l'invention est également susceptible d'être obtenue de la façon suivante :

a) on prépare un sirop de sucre concentré d'environ 60% à environ 97%, notamment 75% en poids de matières sèches,

b) on provoque l'évaporation du sirop par réduction de la pression de manière à atteindre l'ébullition de ce sirop à la température choisie,

c) on brasse le sirop notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, le coefficient de sursaturation du sirop étant compris entre 1 et 1,3, notamment 1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on poursuit l'évaporation dans les mêmes conditions de température et de pression que celles utilisées dans les étapes précédentes, jusqu'à obtention d'un milieu dont les cristaux constituent la phase majoritaire (supérieur à environ 50%, et notamment supérieur à environ 70% par rapport au milieu),

la vitesse d'agitation étant réduite d'environ 50 à environ 200 m/mn, la température étant maintenue constante par rapport aux étapes précédentes, le battage étant maintenu jusqu'à obtention d'un produit sec composé de cristaux de taille souhaitée contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant ajustée et maintenue à une valeur constante dans la gamme allant d'environ 40°C à environ 100°C, notamment d'environ 70°C à environ 100°C, pendant toute la durée des étapes.

L'invention concerne également un procédé de préparation des compositions décrites ci-dessus, lequel procédé est caractérisé par les étapes suivantes :

a) on prépare un sirop concentré,

b) on évapore le sirop sous pression avec agitation vigoureuse dans la zone de cristallisation jusqu'à l'apparition des cristaux, avec contrôle de la température et du débit d'évaporation jusqu'à une teneur en matières sèches d'environ 80% à environ 90%,

c) on poursuit l'évaporation avec réduction de la vitesse d'agitation jusqu'à l'obtention d'un produit sec, la température étant maintenue constante par rapport à l'étape précédente,

la température étant ajustée et maintenue à une valeur déterminée dans l'intervalle d'environ 40°C à environ 100°C, et notamment d'environ 70°C à environ 100°C, pendant la durée des étapes a) à c) décrites ci-dessus.

Ce procédé sera dans la suite désigné par "procédé II".

Selon un mode de réalisation avantageux de l'invention, le procédé II est caractérisé par les étapes suivantes :

a) on prépare un sirop de sucre concentré d'environ 60% à environ 97%, notamment 75% en poids de matières sèches,

b) on provoque l'évaporation du sirop par réduction de la pression de manière à atteindre l'ébullition de ce sirop à la température choisie,

c) on brasse le sirop notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, le coefficient de sursaturation du sirop étant compris entre 1 et 1,3, notamment 1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on poursuit l'évaporation dans les mêmes conditions de température et de pression que celles utilisées dans les étapes précédentes, jusqu'à obtention d'un milieu dont les cristaux constituent la phase majoritaire (supérieur à environ 50%, et notamment supérieur à environ 70% par rapport au milieu),
la vitesse d'agitation étant réduite d'environ 50 à environ 200 m/mn, la température étant maintenue constante par rapport aux étapes précédentes, le battage étant maintenu jusqu'à obtention d'un produit sec composé de cristaux de taille souhaitée contenant moins de 1%, notamment moins de 0,5% d'humidité,
la température étant ajustée et maintenue à une valeur constante dans la gamme allant d'environ 40°C à environ 100°C, notamment d'environ 70°C à environ 100°C, pendant toute la durée des étapes.

Le procédé II commence avec la préparation du sirop concentré de sucre. La concentration adaptée est comprise, à titre indicatif, entre 60 et 80% en poids de matière sèche. Afin d'éviter la recristallisation et la dégradation du sucre ou tout autre produit ajouté à la solution, la température est maintenue de 40°C à 100°C, notamment de 70°C à 100°C. Le sirop est maintenu sous agitation et la pression est abaissée de manière à atteindre l'ébullition du sirop à la température choisie. Cette agitation mécanique ou brassage du sirop est nécessaire à l'homogénéisation du milieu et est réalisée à l'aide d'un mobile d'agitation avantageusement placé en fond de cuve utilisée dans le procédé de l'invention. A titre d'illustration, ce brassage peut être réalisé avec un mélangeur-évaporateur, un cristalliseur, un mélangeur-homogénéiseur, un mélangeur-malaxeur ou tout autre équipement adapté. Il est important que ce brassage soit énergique et que l'énergie apportée au sirop soit contrôlée. En outre, pour le bon fonctionnement du procédé, l'installation doit pouvoir fonctionner sous pression réduite et température régulée.

L'agitation vigoureuse avantageusement effectuée par battage et impact de la solution stimule la formation de germes et un voile est observable après un certain temps.

La concentration du sirop est conduite avec un débit d'évaporation compris entre 20 et 30% par heure de la quantité d'eau initiale. L'évaporation est effectuée sous pression réduite, pression définie par la température du sirop pour obtenir l'ébullition du milieu à cette température.

Le système est maintenu dans cet état d'équilibre débit d'évaporation/pression/température jusqu'à un taux d'évaporation de 65% environ.

Le milieu devient alors très pâteux et, dans cette deuxième étape, la vitesse d'agitation du mobile est abaissée à 190 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec une pression décroissant progressivement pour maintenir une température constante jusqu'à obtention d'une poudre sèche.

Par rapport au procédé I, le procédé II présente les différences suivantes :

. suppression de l'étape d) : "arrêt de l'évaporation et maintien de l'agitation pendant un certain temps",

. le procédé II est avantageusement appliqué aux essais industriels.

Les exemples présentés illustrent l'application du procédé d'invention permettant la fabrication de compositions de cristaux de sucre ayant une taille moyenne comprise entre 80 et 150 μm (Exemples 1 et 2). Par ailleurs, un exemple décrit l'utilisation du procédé pour l'obtention de cristaux de sucre contenant un deuxième composé, en l'occurrence du caramel (Exemple 3).

Les exemples 4 à 6 décrivent respectivement la préparation de glucose, de lactose et d'érythritol selon l'invention.

L'exemple 7 correspond à un essai industriel.

La présente invention décrit une composition de sucre microcristallin dont l'ouverture moyenne est centrée autour de 20 à 220 μm, notamment 20 à 200 μm. La distribution de la taille des cristaux autour de la valeur moyenne est de type gaussien, avec un CV compris entre 20% et 50% ou son indice d'uniformité est compris entre 1 et 5. Les cristaux, de forme régulière, ne sont pas des agglomérats. Les cristaux ont une densité élevée. Le produit est fluide et se dissous rapidement dans l'eau. Les cristaux obtenus par cette méthode ne demandent pas de tamisage particulier autre que l'élimination des agglomérats et particules supérieurs à 300 μm représentant moins de 10% de la composition. La poudre est obtenue avec un bon rendement et une distribution de type gaussien ou présentant un indice d'uniformité compris entre 1 et 5. Comme le procédé pour la fabrication dudit produit est très bien contrôlé, il est possible d'obtenir des cristaux de granulométrie moyenne désirée en modifiant seulement certains paramètres. Par conséquent, la présente invention décrivant des

compositions de sucre microcristallin de diamètre spécifique entre 20 et 220 μm et plus précisément entre 80 et 150 μm est bien démontrée.

Le procédé de la présente invention permet l'addition d'ingrédients désirés au sucre, l'ajout pouvant être fait dans le cadre du procédé I, préférentiellement après formation du voile et avant l'arrêt de l'évaporation, par exemple entre l'étape c) et l'étape d).

Dans le cadre du procédé II, l'ajout peut être fait au moment où la sursaturation atteint une valeur comprise entre 1,0 et 1,3.

On observe, dans ce cas, une co-cristallisation du sucre avec un autre ingrédient. La présente invention décrit également le sucre microcristallin de granulométrie moyenne souhaitée dopé avec un ou des ingrédients choisis. Une large gamme d'ingrédients tels que les gommes, émulsifiants, produits chimiques peuvent être ajoutés. Les cristaux de sucre servent dans ce cas de support pour des ingrédients valorisés, par exemple comme produits alimentaires ou pharmaceutiques, soit pour la couleur, soit pour le goût, ou pour toute autre propriété recherchée.

La présente invention décrit par conséquent des compositions de microcristaux de sucre et d'autres ingrédients.

Le procédé décrit dans la présente invention permet l'utilisation de conditions contrôlées de température. Ainsi, il est possible d'ajouter un second ingrédient thermosensible. Les composés thermosensibles peuvent être des vitamines, aminoacides, caroténoïdes, antibiotiques.

Les cristaux obtenus par la présente invention ont des formes régulières et ne sont pas agglomérés, comme le montre la figure 1. D'une manière générale, et dans les exemples qui suivent, l'ouverture moyenne des cristaux est centrée autour d'une valeur bien déterminée et ceci n'est pas le cas dans les procédés décrits par l'art antérieur. Les exemples suivants illustrent l'invention et ne sont en aucun cas interprétés comme limitant le procédé.

Description des figures :

La figure 1A représente une photographie d'une composition de sucre microcristallin de 80 μm observée au microscope électronique au grossissement X50.

La figure 1B représente une photographie d'une composition de sucre microcristallin de 80 μm observée au microscope électronique au grossissement X150.

La figure 1C représente une photographie d'une composition de sucre glace commercial observée au microscope électronique au grossissement X50.

La figure 1D représente une photographie d'une composition de sucre glace commercial observée au microscope électronique au grossissement X150.

La figure 2 représente la vitesse de dissolution de sucres dans l'eau pure à 18°C. Le temps correspondant à la dissolution totale (exprimé en secondes) est porté sur l'axe des abscisses. Les différents sucres testés sont portés sur l'axe des ordonnées, étant rappelé que le sucre glace a une granulométrie de 80 à 100 μm, que la surfine a une granulométrie de 200 à 250 μm et que les sucres de granulométrie respective de 150 μm et de 80 μm correspondent aux compositions de l'invention.

La figure 3 représente l'indice de coulabilité.

Les produits pulvérulents peuvent former des agglomérats dans les réservoirs de stockage et trémies d'alimentation. Le vidage de ces réservoirs et autres trémies est rendu difficile par ce phénomène, entraînant la formation de voûtes (blocs de poudre restant accrochés aux parois des trémies et au-dessus d'une cavité, et formant des zones mortes), perturbant l'écoulement de la poudre par simple gravité. Il est alors nécessaire d'utiliser tout dispositif mécanique permettant de maintenir cette poudre en mélange homogène, en la stockant sous agitation ou en la soutirant de la trémie à l'aide d'écluses rotatives ou de vibreurs.

La difficulté à manipuler un produit pulvérulent est traduite par son indice de coulabilité qui peut varier de 0 (produit à forte capacité d'agglomération, mottant, collant) à 100 (produit extrêmement fluide de comportement proche de celui d'un liquide).

Les faibles indices nécessitent un équipement spécial adapté à chaque cas, les forts indices ne posant pas de problème particulier en stockage et manutention.

La figure 4 représente un schéma de principe de l'appareillage utilisé dans le cadre des exemples 1 à 7.

L'appareillage utilisé peut être constitué par un évaporateur mélangeur constitué d'une enceinte (1) susceptible de fonctionner sous pression réduite et température régulée. A cette fin, cette enceinte comporte un fluide caloporteur.

(2), dont la prise d'entrée est par exemple en 2a et la prise de sortie en 2b, et est reliée à une prise de vide (3).

Le mélange (ou brassage) du sirop de sucre au cours du procédé est assuré par un mobile d'agitation (4).

Le battage par impact est effectué par exemple par un couteau émotteur télescopique (5).

Exemple 1 :

Préparation de sucre microcristallin d'ouverture moyenne 80 μm et de CV = 40%.

Vingt kg de sucre sont mis en solution dans 6 kg d'eau à 80°C, température qui sera maintenue constante tout au long de la préparation.

La vitesse de brassage est fixée à 245 m/min (vitesse périphérique). L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,3 et avantageusement 1,2 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte. Le débit d'évaporation est maintenu à une valeur de 1,5 l/h sous 250 mbars.

Après 15 mn dans ces conditions, un voile blanc significatif de la nucléation apparaît dans le milieu. Cet état est maintenu pendant 40 mn, l'action de l'émotteur permettant de multiplier le nombre de germes en limitant leur croissance.

L'évaporation et le battage sont stoppés pendant 10 minutes, pour laisser la place à une phase de croissance cristalline régulière.

Dans la dernière étape, la vitesse d'agitation du mobile de brassage est fixée à 190 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à l'obtention d'une poudre sèche.

Durée globale de l'opération : 3 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes :

vitesse de dissolution : 7 sec.

indice de coulabilité : 81

densité de la composition tassée : 0,97

densité de la composition non tassée : 0,83.

Exemple 2 :

Préparation de sucre microcristallin d'ouverture moyenne 150 µm et de CV = 30%.

Vingt kg de sucre sont dissous dans 6 kg d'eau à 80°C, température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 135 m/mn (vitesse périphérique). L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,3 et avantageusement 1,2 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte.

Le débit d'évaporation est maintenu à une valeur de 1,5 l/h sous 250 mbars.

Après 10 mn dans ces conditions, un voile blanc significatif de la nucléation apparaît dans le milieu. Cet état est maintenu pendant 5 mn, puis l'évaporation et l'émotteur sont stoppés pendant 15 minutes, favorisant la phase de croissance cristalline.

Dans la deuxième étape, la vitesse d'agitation du mobile de brassage est fixée à 135 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à l'obtention d'une poudre sèche.

Durée globale de l'opération : 5 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes :

vitesse de dissolution : 9 sec.

indice de coulabilité : 82

densité de la composition tassée : 1,00

densité de la composition non tassée : 0,87.

Exemple 3 :

Préparation de sucre microcristallin d'ouverture moyenne 150 µm et de CV = 30% contenant du caramel.

Vingt kg de sucre sont dissous dans 6 kg d'eau à 80°C, température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 135 m/mn (vitesse périphérique). L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,3 et avantageusement 1,2 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte.

Le débit d'évaporation est maintenu à une valeur de 1,5 l/h sous 250 mbars.

A cet instant, 400 g de caramel aromatique représentant 2% de la masse totale de sucre sont dilués dans le milieu.

Après 5 minutes d'homogénéisation, l'évaporation et l'émotteur sont stoppés pendant 15 minutes, favorisant la phase de croissance cristalline.

Dans la dernière étape, la vitesse d'agitation du mobile de brassage est fixée à 135 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à l'obtention d'une poudre sèche.

Durée globale de l'opération : 5 heures.

La composition de l'invention ainsi obtenue a les mêmes caractéristiques que la composition obtenue à l'exemple 2.

Exemple 4 :

Préparation de glucose microcristallin d'ouverture moyenne 75 μm.

Dix huit kg de glucose sont dissous dans 5,4 kg d'eau à 70°C. température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 245 m/mn (vitesse périphérique).

L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,4 et avantageusement de 1,3 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte. Le débit d'évaporation est maintenu à une valeur moyenne de 1,5 l/h sous environ 180 mbars.

Après 100 mn dans ces conditions, un voile blanc significatif de la nucléation apparaît dans le milieu. Cet état est maintenu pendant 40 mn, l'action de l'émotteur permettant de multiplier le nombre de germes en limitant la croissance.

L'évaporation et le battage sont stoppés pendant 10 minutes, favorisant la phase de croissance cristalline.

Dans la deuxième étape, la vitesse d'agitation du mobile est fixée à 140 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à obtention d'une poudre sèche.

Durée globale de l'opération : 4 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes :

- indice de coulabilité : 60
- densité de la composition tassée : 0,75
- densité de la composition non tassée : 0,52.

Exemple 5 :

Préparation de lactose microcristallin d'ouverture moyenne 50 µm.

Quinze kg de lactose sont dissous dans 20 kg d'eau à 72°C, température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 245 m/mn (vitesse périphérique).

L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,3 et avantageusement de 1,1 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte. Le débit d'évaporation est maintenu à une valeur moyenne de 2,5 l/h sous environ 180 mbars.

Après 220 mn dans ces conditions, un voile blanc significatif de la nucléation apparaît dans le milieu. Ce état est maintenu pendant 40 mn, l'action de l'émotteur permettant de multiplier le nombre de germes en limitant la croissance.

L'évaporation et le battage sont stoppés pendant 10 minutes, favorisant la phase de croissance cristalline.

Dans la deuxième étape, la vitesse d'agitation du mobile est fixée à 140 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à obtention d'une poudre sèche.

Durée globale de l'opération : 7 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes :

- vitesse de dissolution : non soluble dans les conditions de l'essai
- indice de coulabilité : 80
- densité de la composition tassée : 0,93
- densité de la composition non tassée : 0,83.

Exemple 6 :

Préparation d'érythritol microcristallin d'ouverture moyenne 220 µm.

Dix huit kg d'érythritol sont dissous dans 8 kg d'eau à 70°C, température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 245 m/mn (vitesse périphérique).

L'évaporation du sirop est conduite jusqu'à une sursaturation d'une valeur comprise entre 1,1 et 1,3 et avantageusement de 1,1 et l'action de l'émotteur (environ 1000 tours/mn) est effective dès que la valeur de la sursaturation déterminée est atteinte. Le débit d'évaporation est maintenu à une valeur moyenne de 2,0 l/h sous environ 180 mbars.

Après 40 mn dans ces conditions, un voile blanc significatif de la nucléation apparaît dans le milieu.

L'évaporation et le battage sont stoppés pendant 10 minutes, favorisant la phase de croissance cristalline.

Dans la deuxième étape, la vitesse d'agitation du mobile est fixée à 140 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec un débit croissant jusqu'à obtention d'une poudre sèche.

Durée globale de l'opération : 3,5 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes :

- vitesse de dissolution : non soluble dans les conditions de l'essai (trouble persistant)
- indice de coulabilité : 83
- densité de la composition tassée : 0,92
- densité de la composition non tassée : 0,90.

Exemple 7 :

Essai industriel.

Préparation de saccharose microcristallin d'ouverture moyenne 120 μm.

Dans un mélangeur Guedu de 1600 litres, 800 kg de saccharose sont dissous dans 310 kg d'eau à 62°C, température qui sera maintenue constante tout au long de l'opération.

La vitesse d'agitation du mobile de brassage est fixée à 330 m/mn (vitesse périphérique).

L'action de l'émotteur (environ 1000 tours/mn) est effective dès le début de l'évaporation et tout au long de l'opération. La concentration du sirop est conduite avec un débit d'évaporation moyen de 20 à 30%/heure. L'énergie apportée au système (chauffage vapeur, double enveloppe) est régulée par la consigne de débit prédéterminé.

L'évaporation est effectuée sous pression réduite, pression définie par la température du sirop pour obtenir l'ébullition du milieu à cette température.

Le système est maintenu dans cet état d'équilibre, débit d'évaporation/pression/température jusqu'à un taux d'évaporation de 65% environ.

Le milieu devient alors très pâteux et, dans cette deuxième étape, la vitesse d'agitation du mobile est abaissée à 190 m/mn (vitesse périphérique) et l'évaporation est poursuivie avec une pression décroissant progressivement pour maintenir une température constante jusqu'à obtention d'une poudre sèche.

En fin de cycle, le produit est déchargé sans refroidissement préalable, les grugeons éventuellement présents dans la poudre sont éliminés par passage rapide sur un tamis de 300 μm. Les cristaux obtenus ne mottent pas après plusieurs jours de stockage à l'air ambiant.

Durée globale de l'opération : 6 heures.

La composition de l'invention ainsi obtenue a les propriétés suivantes:

- vitesse de dissolution : 8 sec.
- indice de coulabilité : 82
- densité de la composition tassée : 0,98
- densité de la composition non tassée : 0,84.

FEUILLE DE REMPLACEMENT (REGLE 26)

Exemple comparatif :

	Sucre glace	Semoule surfine	Exemple 1 saccharose	Exemple 2 saccharose	Exemple 3 saccharose	Exemple 4 glucose	Exemple 5 lactose	Exemple 6 érythritol	Exemple 7 saccharose
OM (µm)	< 80	250	80	150	150	75	50	220	120
C.V. (%)	N.D.*	N.D.*	35-45	30-40	30-40	N.D.*	N.D.*	N.D.*	50
Indice de coulabilité	42	75	81	82	82	60	80	83	82
Vitesse de dissolution (sec.)	22**	13	7	9	9	N.D.*	N.D.*	N.D.*	8
Densité produit non tassé	0,45	0,65	0,83	0,87	0,87	0,52	0,83	0,90	0,84
Densité produit tassé	0,88	0,87	0,97	1,00	1,00	0,75	0,93	0,92	0,98
Mottage	oui	non motté	non motté	non motté	non motté	non motté	non motté	non motté	non motté

* N.D. : non déterminé

** : problème de mouillabilité

REVENDICATIONS

1. Composition contenant des microcristaux de sucre caractérisée en ce que les cristaux sont essentiellement des monocristaux de forme géométrique régulière, ne présentant pas de brisure, homogènes les uns par rapport aux autres, et en ce que

- la granulométrie suit une distribution gaussienne dont la médiane est d'environ 20 μm à environ 220 μm, notamment d'environ 20 μm à environ 200 μm, le coefficient de variation étant d'environ 20% à environ 50%, notamment d'environ 30% à 45%, ou d'environ 35% à 45%, ou d'environ 30% à 40% ou

- la répartition granulométrique est caractérisée par un indice d'uniformité compris entre 1 et 5, notamment entre 2.5 et 3.5.

2. Composition selon la revendication 1, caractérisée en ce qu'elle présente les propriétés suivantes :

- sa vitesse de dissolution est d'environ 5 à environ 10, notamment d'environ 7 à environ 9 secondes, dans les conditions suivantes : 10 g de composition pour 100 ml d'eau pure déminéralisée, à la température de 18°C,

- elle est non mottante,

- son indice de coulabilité est supérieur à environ 80, et varie d'environ 80 à environ 85, notamment d'environ 81 à environ 82, mesuré selon le test d'Hosakawa, tel que décrit dans IRON WORKS, LTD, Osaka, Japon, et lorsqu'il s'agit du glucose, l'indice de coulabilité est d'environ 55 à environ 70,

- la densité du produit tassé est d'environ 0,90 à environ 1,00, notamment d'environ 0,97 à environ 1,00, et la densité du produit non tassé est d'environ 0,75 à environ 0,90, notamment d'environ 0,83 à environ 0,87, mesurées selon le test d'Hosakawa, et lorsque le susdit produit est du glucose, la densité du produit tassé est d'environ 0,70 à environ 0,90 et la densité du produit non tassé est d'environ 0,50 à environ 0,70.

3. Composition selon l'une des revendications 1 ou 2, caractérisée en ce qu'elle contient des ingrédients additionnels, à raison d'environ 0% à environ 10%, et avantageusement à raison d'environ 5%, ces ingrédients étant de façon avantageuse choisis parmi les composés thermosensibles, des composés ayant

des propriétés alimentaires ou pharmacologiques, ou des composés ayant un goût ou une couleur recherchés.

4. Composition selon l'une des revendications 1 à 3, susceptible d'être obtenue par le procédé comprenant les étapes suivantes :

a) on prépare un sirop de saccharose concentré, d'environ 60 à environ 97, notamment 75% en poids de matières sèches,

b) on réduit la pression qui passe de la pression atmosphérique à une valeur d'environ 100 à environ 300 mbars, notamment d'environ 200 mbars, pour commencer à évaporer une partie de l'eau contenue dans le sirop de sucre, le taux d'évaporation étant d'environ 20%,

c) on évapore une partie de l'eau contenue dans le sirop de sucre sous pression réduite (environ 200 mbars) et on brasse le sirop, notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, jusqu'à atteindre un coefficient de sursaturation de sucre compris entre 1,1 et 1,3 et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on effectue la suite de la cristallisation par arrêt de l'évaporation et de l'agitation vigoureuse (battage), et maintien d'une agitation régulière (brassage) pendant le temps nécessaire à l'obtention des cristaux de taille souhaitée, et avantageusement pendant environ 5 mn à environ 20 mn,

e) on reprend l'évaporation (toujours avec brassage du milieu à une vitesse d'environ 100 à environ 350 m/mn) jusqu'à l'obtention de cristaux contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant maintenue à une valeur d'environ 70°C à environ 100°C, pendant toute la durée du procédé, et la pression étant avantageusement maintenue à environ 200 mbars pendant les étapes c) à e).

5. Composition selon l'une quelconque des revendications 1 à 3, susceptible d'être obtenue par le procédé comprenant les étapes suivantes :

a) on prépare un sirop de sucre concentré d'environ 60% à environ 97%, notamment 75% en poids de matières sèches,

b) on provoque l'évaporation du sirop par réduction de la pression de manière à atteindre l'ébullition de ce sirop à la température choisie,

c) on brasse le sirop notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, le coefficient de sursaturation du sirop étant compris entre 1 et 1,3, notamment

1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on poursuit l'évaporation dans les mêmes conditions de température et de pression que celles utilisées dans les étapes précédentes, jusqu'à obtention d'un milieu dont les cristaux constituent la phase majoritaire (supérieur à environ 50%, et notamment supérieur à environ 70% par rapport au milieu),
la vitesse d'agitation étant réduite d'environ 50 à environ 200 m/mn, la température étant maintenue constante par rapport aux étapes précédentes, le battage étant maintenu jusqu'à obtention d'un produit sec composé de cristaux de taille souhaitée contenant moins de 1%, notamment moins de 0,5% d'humidité,
la température étant ajustée et maintenue à une valeur constante dans la gamme allant d'environ 40°C à environ 100°C, notamment d'environ 70°C à environ 100°C, pendant toute la durée des étapes.

6. Procédé de préparation d'une composition selon l'une quelconque des revendications 1 à 4, caractérisé par les étapes suivantes :

a) on prépare un sirop de saccharose concentré, d'environ 60 à environ 97, notamment 75% en poids de matières sèches,

b) on réduit la pression qui passe de la pression atmosphérique à une valeur d'environ 100 à environ 300 mbars, notamment d'environ 200 mbars, pour commencer à évaporer une partie de l'eau contenue dans le sirop de sucre, le taux d'évaporation étant d'environ 20%,

c) on évapore une partie de l'eau contenue dans le sirop de sucre sous pression réduite (environ 200 mbars) et on brasse le sirop, notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, jusqu'à atteindre un coefficient de sursaturation de sucre compris entre 1,1 et 1,3 et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on effectue la suite de la cristallisation par arrêt de l'évaporation et de l'agitation vigoureuse (battage), et maintien d'une agitation régulière (brassage) pendant le temps nécessaire à l'obtention des cristaux de taille souhaitée, et avantageusement pendant environ 5 mn à environ 20 mn,

e) on reprend l'évaporation (toujours avec brassage du milieu à une vitesse d'environ 100 à environ 350 m/mn) jusqu'à l'obtention de cristaux contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant maintenue à une valeur d'environ 70°C à environ 100°C, pendant toute la durée du procédé, et la pression étant avantageusement maintenue à environ 200 mbars pendant les étapes c) à e).

7. Procédé de préparation d'une composition selon l'une quelconque des revendications 1 à 3 et 5, caractérisé par les étapes suivantes :

a) on prépare un sirop de sucre concentré d'environ 60% à environ 97%, notamment 75% en poids de matières sèches,

b) on provoque l'évaporation du sirop par réduction de la pression de manière à atteindre l'ébullition de ce sirop à la température choisie,

c) on brasse le sirop notamment par agitation mécanique à une vitesse périphérique d'environ 100 à environ 350 m/mn, notamment 200 à 350 m/mn, le coefficient de sursaturation du sirop étant compris entre 1 et 1,3, notamment 1,1 et 1,3, et on provoque la cristallisation par une agitation vigoureuse du sirop (en plus du brassage susmentionné), notamment par chocs mécaniques générés par battage par impact, dans cette zone de sursaturation,

d) on poursuit l'évaporation dans les mêmes conditions de température et de pression que celles utilisées dans les étapes précédentes, jusqu'à obtention d'un milieu dont les cristaux constituent la phase majoritaire (supérieur à environ 50%, et notamment supérieur à environ 70% par rapport au milieu),

la vitesse d'agitation étant réduite d'environ 50 à environ 200 m/mn, la température étant maintenue constante par rapport aux étapes précédentes, le battage étant maintenu jusqu'à obtention d'un produit sec composé de cristaux de taille souhaitée contenant moins de 1%, notamment moins de 0,5% d'humidité,

la température étant ajustée et maintenue à une valeur constante dans la gamme allant d'environ 40°C à environ 100°C, notamment d'environ 70°C à environ 100°C, pendant toute la durée des étapes.

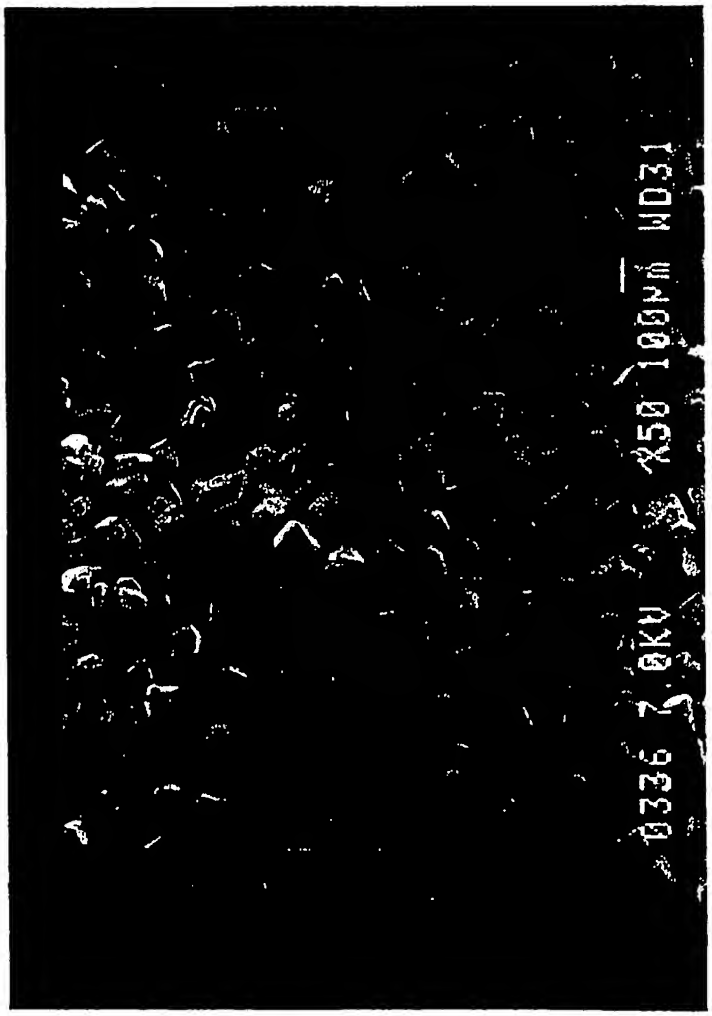

Figure 1A

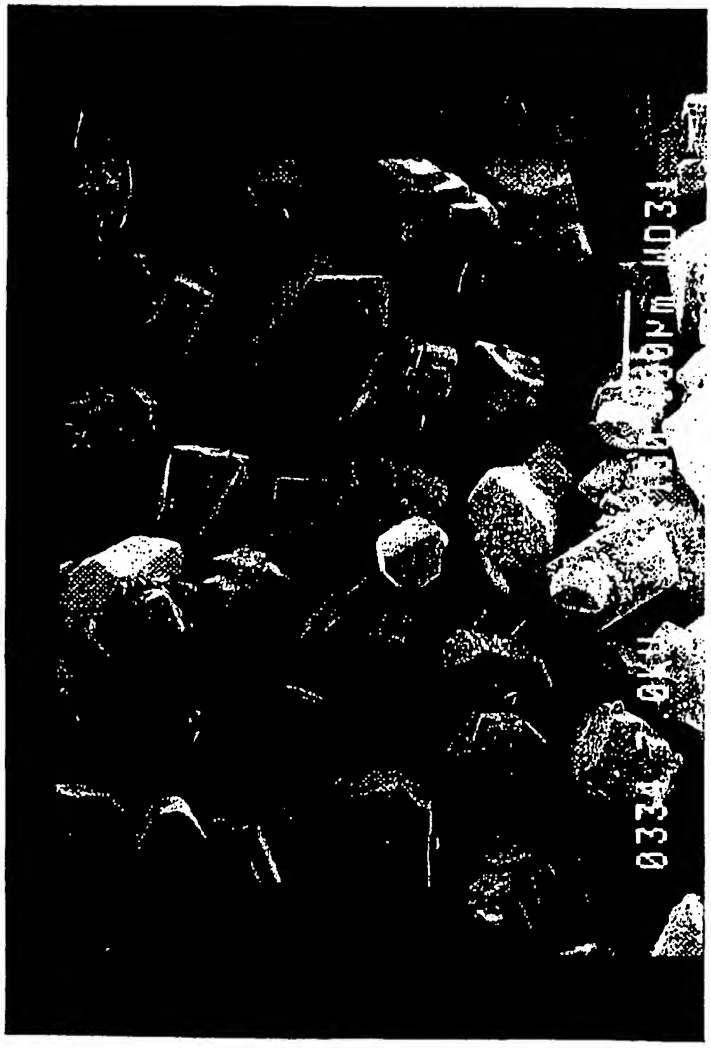

Figure 1B

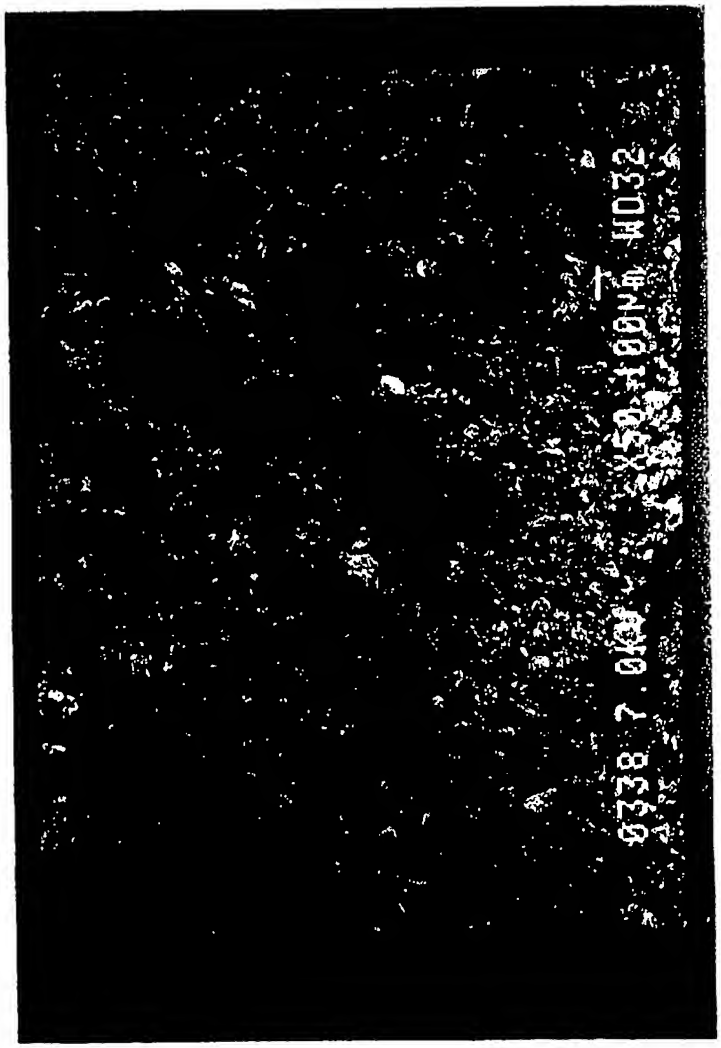

Figure 1C

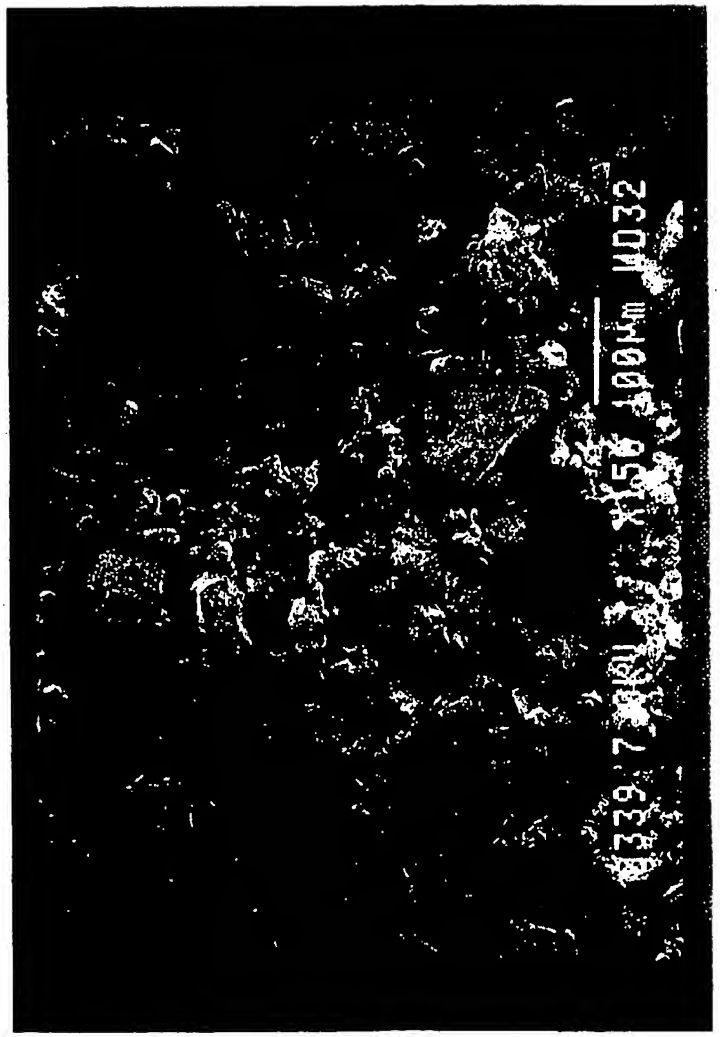

Figure 1D

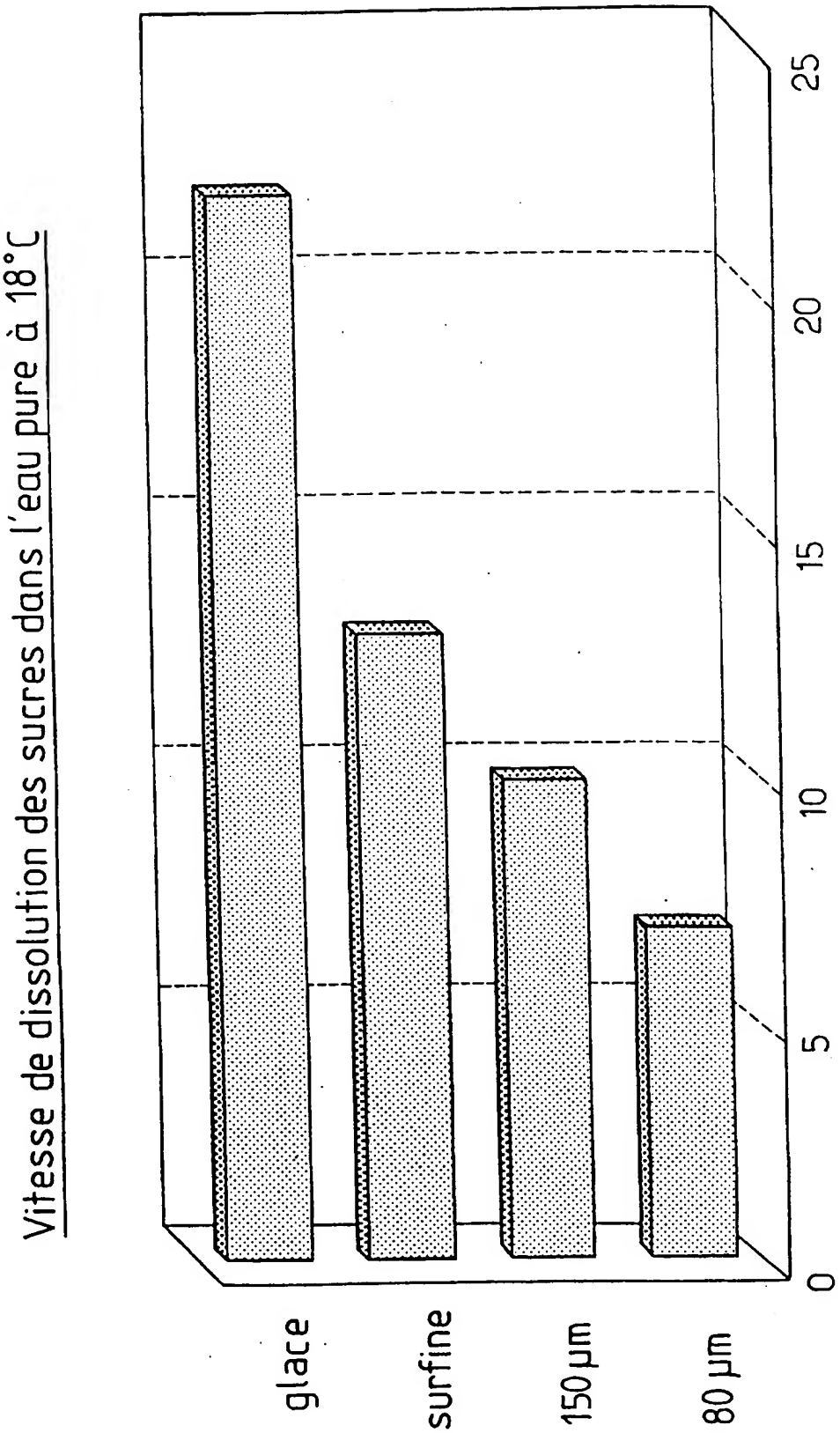
Vitesse de dissolution des sucres dans l'eau pure à 18°C
0
5
10
15
20
25
temps à la dissolution totale (sec.)
glace
surfine
150 µm
80 µm

FIG. 2

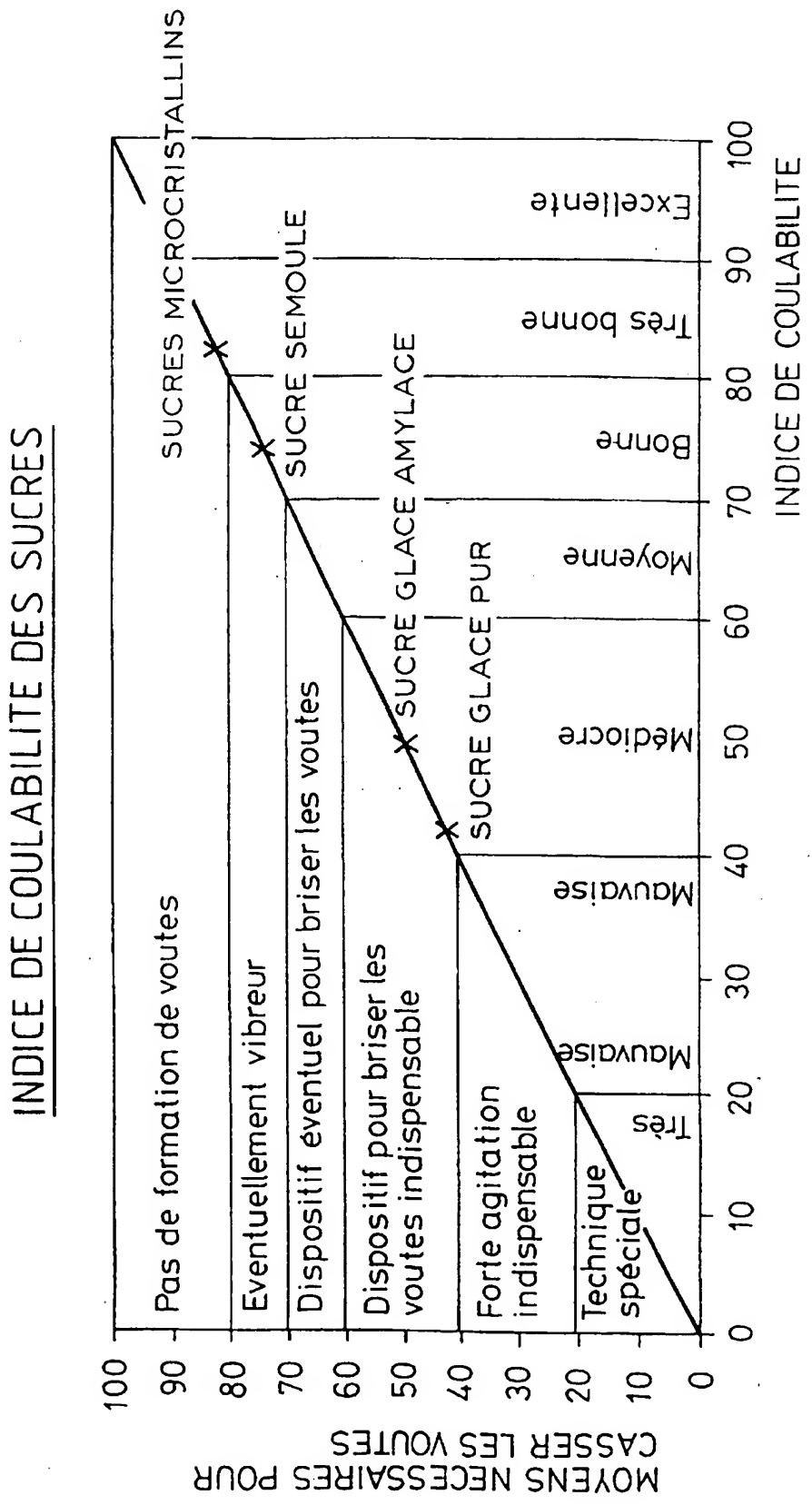
INDICE DE COULABILITE DES SUCRES
MOYENS NECESSAIRES POUR CASSER LES VOUTES
INDICE DE COULABILITE
0
10
20
30
40
50
60
70
80
90
100
Pas de formation de voutes
Eventuellement vibreur
Dispositif éventuel pour briser les voutes
Dispositif pour briser les voutes indispensable
Forte agitation indispensable
Technique spéciale
Très Mauvaise
Mauvaise
Médiocre
Moyenne
Bonne
Très bonne
Excellente
SUCRES MICROCRISTALLINS
SUCRE SEMOULE
SUCRE GLACE AMYLACE
SUCRE GLACE PUR

FIG. 3

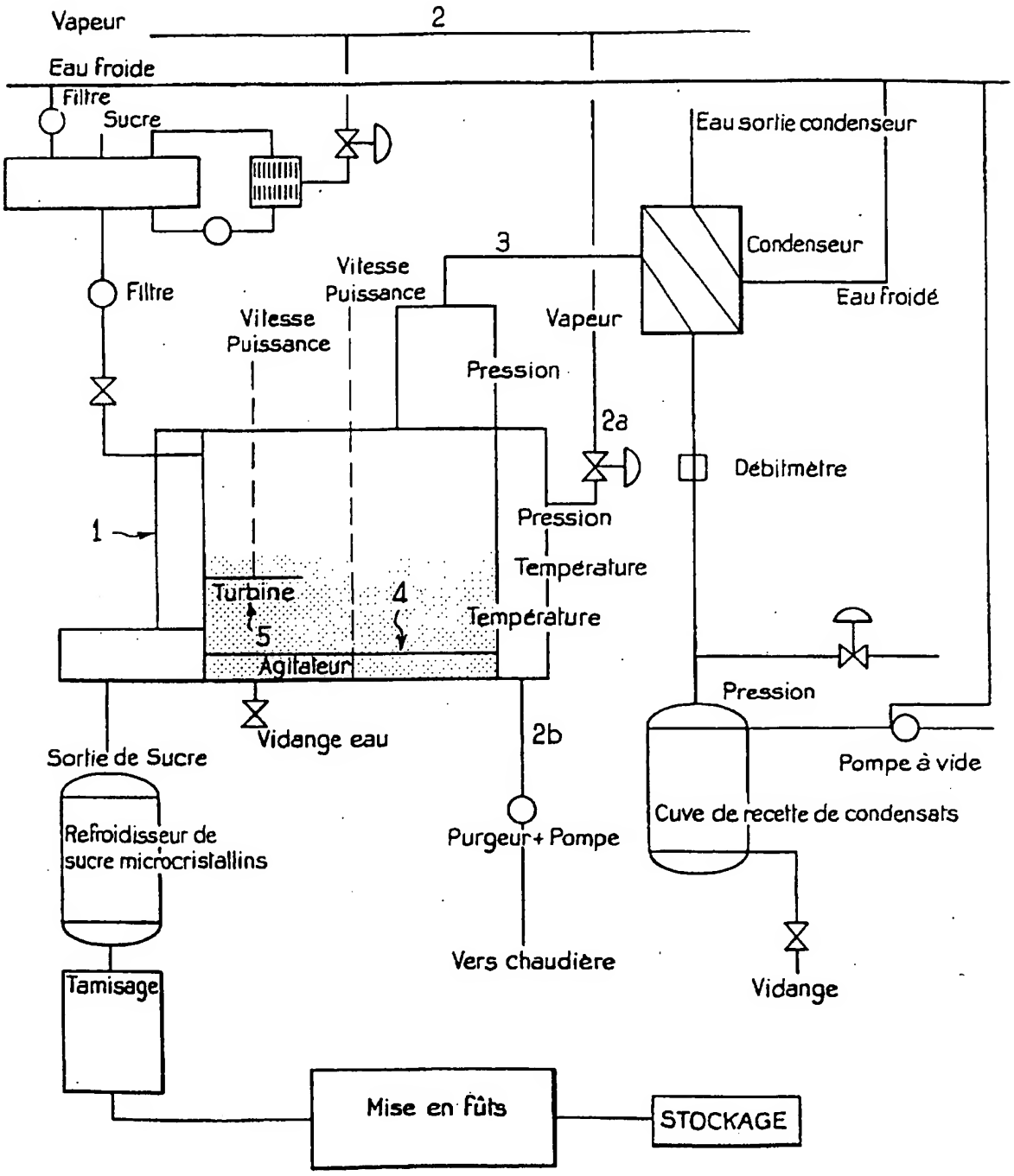
Vapeur
2
Eau froide
Filtre
Sucre
Eau sortie condenseur
3
Condenseur
Vitesse
Puissance
Filtre
Eau froide
Vitesse
Puissance
Vapeur
Pression
2a
Débitmètre
Pression
1
Température
Turbine
4
Température
5
Agitateur
Pression
Vidange eau
2b
Sortie de Sucre
Pompe à vide
Refroidisseur de
sucre microcristallins
Purgeur+ Pompe
Cuve de recette de condensats
Vers chaudière
Vidange
Tamisage
Mise en fûts
STOCKAGE

FIG_4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 96/01931

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C13F1/02 C13F3/00 C07H3/04 C07H1/06 C13K1/10
C13K5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C13F C07H C13K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 38 42 751 A (GEA WIEGAND) 5 July 1990 see claim 1	1-3
A	FR 2 669 511 A (EUROSUCRE S.N.C. ET GENERALE SUCRIERE) 29 May 1992 see claims	1-3
A	EP 0 052 919 A (AMSTAR) 2 June 1982 see claims	1-7
A	FR 2 244 411 A (GENERAL FOODS) 18 April 1975 see claims	1-3
A	US 3 194 682 A (D.E.TIPPENS ET AL.) 13 July 1965 cited in the application see claims	1-7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 1997	16.05.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Moer, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 96/01931

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 365 331 A (M.D.MILLER ET AL.) 23 January 1968 cited in the application see claims	1-7
A	EP 0 052 413 A (AMSTAR) 26 May 1982 cited in the application see claims	1-7
A	DE 19 10 752 A (WHITING) 6 November 1969 see claims	1-7
A	EP 0 039 123 A (TATE 6 LYLE) 4 November 1981 see claims; examples	1-3,5,7
X	WO 91 11179 A (NATIONAL RESEARCH DEVELOPMENT) 8 August 1991 see claims see page 3, line 3-14	1-3

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 96/01931

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,3,5,7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

A complete search concerning the "mono-, di and oligosaccharides as well as the polyols produced by their reduction", as defined on page 3, lines 16-17 of the description, is effectively impossible.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

The search has thus been carried out with respect to the "sugars" cited in the examples: saccharose, glucose, lactose and erythritol.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FR 96/01931

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3842751 A	05-07-90	NONE	
FR 2669511 A	29-05-92	BE 1006586 A	18-10-94
		DE 4138869 A	04-06-92
		IT 1252719 B	26-06-95
		LU 88036 A	01-06-92
		NL 9101950 A	16-06-92
EP 52919 A	02-06-82	US 4338350 A	06-07-82
		CA 1154628 A	04-10-83
		JP 1337633 C	29-09-86
		JP 57122759 A	30-07-82
		JP 60056478 B	10-12-85
FR 2244411 A	18-04-75	US 3843822 A	22-10-74
		US 3898347 A	05-08-75
		AR 219041 A	31-07-80
		AU 6276073 A	22-05-75
		CA 1012967 A	28-06-77
		CH 588219 A	31-05-77
		DE 2359250 A	03-04-75
		GB 1446929 A	18-08-76
		JP 50058270 A	21-05-75
		NL 7316325 A	26-03-75
		AR 221316 A	30-01-81
		AU 7027074 A	08-01-76
		CA 980170 A	23-12-75
		DE 2430103 A	23-01-75
		FR 2235650 A	31-01-75
		JP 1106521 C	30-07-82
		JP 50036670 A	05-04-75
		JP 56050553 B	30-11-81
		NL 7408662 A	06-01-75
US 3194682 A	13-07-65	NONE	
US 3365331 A	23-01-68	FR 1559088 A	07-03-69
		GB 1163694 A	10-09-69
EP 52413 A	26-05-82	US 4362757 A	07-12-82

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/FR 96/01931

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 52413 A		CA 1154627 A	04-10-83
		JP 1337632 C	29-09-86
		JP 57138400 A	26-08-82
		JP 60056477 B	10-12-85
DE 1910752 A	06-11-69	FR 2004494 A	28-11-69
		GB 1268563 A	29-03-72
		NL 6904428 A	24-09-69
		US 3503803 A	31-03-70
EP 39123 A	04-11-81	AT 9716 T	15-10-84
		CA 1171853 A	31-07-84
		GB 2070015 A,B	03-09-81
		JP 1397479 C	24-08-87
		JP 56137900 A	28-10-81
		JP 61052680 B	14-11-86
		US 4342603 A	03-08-82
WO 9111179 A	08-08-91	AU 635616 B	25-03-93
		AU 7155991 A	21-08-91
		CA 2049302 A	25-07-91
		DE 69100792 D	27-01-94
		DE 69100792 T	14-04-94
		EP 0464171 A	08-01-92
		GB 2240337 A,B	31-07-91
		JP 4504427 T	06-08-92
		US 5254330 A	19-10-93
		US 5376386 A	27-12-94

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No
PCT/FR 96/01931

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 C13F1/02 C13F3/00 C07H3/04 C07H1/06 C13K1/10
C13K5/00

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 C13F C07H C13K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si cela est réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	DE 38 42 751 A (GEA WIEGAND) 5 Juillet 1990 voir revendication 1	1-3
A	FR 2 669 511 A (EUROSUCRE S.N.C. ET GENERALE SUCRIERE) 29 Mai 1992 voir revendications	1-3
A	EP 0 052 919 A (AMSTAR) 2 Juin 1982 voir revendications	1-7
A	FR 2 244 411 A (GENERAL FOODS) 18 Avril 1975 voir revendications	1-3

-/--

[X] Voir la suite du cadre C pour la fin de la liste des documents

[X] Les documents de familles de brevets sont indiqués en annexe

* Catégories spéciales de documents cités:

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

1

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
21 Avril 1997	16.05.97

Nom et adresse postale de l'administration chargée de la recherche internationale	Fonctionnaire autorisé
Office Européen des Brevets, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Van Moer, A

Formulaire PCT/ISA/210 (deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No
PCT/FR 96/01931

C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
A	US 3 194 682 A (D.E.TIPPENS ET AL.) 13 Juillet 1965 cité dans la demande voir revendications	1-7
A	US 3 365 331 A (M.D.MILLER ET AL.) 23 Janvier 1968 cité dans la demande voir revendications	1-7
A	EP 0 052 413 A (AMSTAR) 26 Mai 1982 cité dans la demande voir revendications	1-7
A	DE 19 10 752 A (WHITING) 6 Novembre 1969 voir revendications	1-7
A	EP 0 039 123 A (TATE 6 LYLE) 4 Novembre 1981 voir revendications; exemples	1-3,5,7
X	WO 91 11179 A (NATIONAL RESEARCH DEVELOPMENT) 8 Août 1991 voir revendications voir page 3, ligne 3-14	1-3

1

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale n°

PCT/FR 96/01931

Cadre I Observations - lorsqu'il a été estimé que certaines revendications ne pouvaient pas faire l'objet d'une recherche (suite du point 1 de la première feuille)

Conformement à l'article 17.2)a), certaines revendications n'ont pas fait l'objet d'une recherche pour les motifs suivants:

1. ☐ Les revendications n°s
se rapportent à un objet à l'égard duquel l'administration n'est pas tenue de procéder à la recherche, à savoir:

2. ☒ Les revendications n°s 1,2,3,5,7
se rapportent à des parties de la demande internationale qui ne remplissent pas suffisamment les conditions prescrites pour qu'une recherche significative puisse être effectuée, en particulier:

Une recherche complete portant sur les "mono-,di- et oligosaccharides, ainsi que les polyols obtenus par réduction de ceux-ci", ainsi qu'ils sont définis page 3, ligne 16 et 17 de la description, est matériellement impossible.

3. ☐ Les revendications n°s
sont des revendications dépendantes et ne sont pas rédigées conformément aux dispositions de la deuxième et de la troisième phrases de la règle 6.4.a).

Cadre II Observations - lorsqu'il y a absence d'unité de l'invention (suite du point 2 de la première feuille)

L'administration chargée de la recherche internationale a trouvé plusieurs inventions dans la demande internationale, à savoir:

1. ☐ Comme toutes les taxes additionnelles ont été payées dans les délais par le déposant, le présent rapport de recherche internationale porte sur toutes les revendications pouvant faire l'objet d'une recherche.

2. ☐ Comme toutes les recherches portant sur les revendications qui s'y prêtaient ont pu être effectuées sans effort particulier justifiant une taxe additionnelle, l'administration n'a sollicité le paiement d'aucune taxe de cette nature.

3. ☐ Comme une partie seulement des taxes additionnelles demandées a été payée dans les délais par le déposant, le présent rapport de recherche internationale ne porte que sur les revendications pour lesquelles les taxes ont été payées, à savoir les revendications n°s:

4. ☐ Aucune taxe additionnelle demandée n'a été payée dans les délais par le déposant. En conséquence, le présent rapport de recherche internationale ne porte que sur l'invention mentionnée en premier lieu dans les revendications; elle est couvertes par les revendications n°s:

Remarque quant à la réserve

☐ Les taxes additionnelles étaient accompagnées d'une réserve de la part du déposant.

☐ Le paiement des taxes additionnelles n'était assorti d'aucune réserve.

SUITE DES RENSEIGNEMENTS INDIQUES SUR PCT/ISA/ 210

La recherche a donc porté sur les "sucres" cités dans les exemples: saccharose, glucose, lactose et érythritol.

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande Internationale No
PCT/FR 96/01931

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
DE 3842751 A	05-07-90	AUCUN	
FR 2669511 A	29-05-92	BE 1006586 A	18-10-94
		DE 4138869 A	04-06-92
		IT 1252719 B	26-06-95
		LU 88036 A	01-06-92
		NL 9101950 A	16-06-92
EP 52919 A	02-06-82	US 4338350 A	06-07-82
		CA 1154628 A	04-10-83
		JP 1337633 C	29-09-86
		JP 57122759 A	30-07-82
		JP 60056478 B	10-12-85
FR 2244411 A	18-04-75	US 3843822 A	22-10-74
		US 3898347 A	05-08-75
		AR 219041 A	31-07-80
		AU 6276073 A	22-05-75
		CA 1012967 A	28-06-77
		CH 588219 A	31-05-77
		DE 2359250 A	03-04-75
		GB 1446929 A	18-08-76
		JP 50058270 A	21-05-75
		NL 7316325 A	26-03-75
		AR 221316 A	30-01-81
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US 3365331 A	23-01-68	FR 1559088 A	07-03-69
		GB 1163694 A	10-09-69
EP 52413 A	26-05-82	US 4362757 A	07-12-82

RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Demande Internationale No
PCT/FR 96/01931

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
EP 52413 A		CA 1154627 A	04-10-83
		JP 1337632 C	29-09-86
		JP 57138400 A	26-08-82
		JP 60056477 B	10-12-85
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		CA 1171853 A	31-07-84
		GB 2070015 A,B	03-09-81
		JP 1397479 C	24-08-87
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		GB 2240337 A,B	31-07-91
		JP 4504427 T	06-08-92
		US 5254330 A	19-10-93
		US 5376386 A	27-12-94

PATENT COOPERATION TREATY

RECEIVED

FEB 14 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

Woodard, Emhardt, Naughton, Moriarty & McNett

To:
HENRY, Thomas Q.
WOODARD, EMHARDT, NAUGHTON,
MORIARTY & McNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*: 08.02.01

Applicant's or agent's file reference: 7040339LLY54

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 00/16140	12/06/2000	11/06/1999

Applicant: ELI LILLY AND COMPANY et al.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   10/01/2001

2. This date of receipt is:

   - [x] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
   - [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
   - [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   [ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

CHAVONAND F H

Tel. (+49-89) 2399-2390

EUROPÄISCHES PATENTAMT · EUROPEAN PATENT OFFICE · OFFICE EUROPÉEN DES BREVETS

Form PCT/IPEA/402 (July 1998) P20452 (05/02/2001)

PATENT COOPERATION TREATY

RECEIVED

DEC 2 0 2000

Woodard, Emhardt, Naughton, Moriarty & McNett

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
WOODARD, EMHARDT, NAUGHTON,
MORIARTY & McNETT
Attn. HENRY, Thomas
Bank One Center/Tower, suite 3700
111 Monument Circle
INDIANAPOLIS, INDIANA 46204
UNITED STATES OF AMERICA

Applicant's or agent's file reference 7040339LLY54	Date of mailing *(day/month/year)* 13/12/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 00/16140	International filing date *(day/month/year)* 12/06/2000
Applicant ELI LILLY AND COMPANY	ENTERED 2-13-01

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Catherine Humbert

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

BNSDOCID: <XSISA220NOENP4_1_>

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

BNSDOCID: <XSISA220NOENP4_1_>

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
7040339LLY54		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/16140	12/06/2000	11/06/1999
Applicant		
ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 2

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 21838 A (ERIDANIA BEGHIN-SAY,FR) 19 June 1997 (1997-06-19) claims page 10, line 3 - line 18	1,7,10, 12-14
A	EP 0 119 480 A (BASF) 26 September 1984 (1984-09-26) claims	1-14
A	EP 0 314 469 A (FUJITSU LTD.,JP) 3 May 1989 (1989-05-03) claims	1-14
A	EP 0 435 450 A (ICI AMERICAS) 3 July 1991 (1991-07-03) cited in the application claims	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2000	13/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 160 100 A (SANDOZ) 18 December 1985 (1985-12-18) claims	1-14
A	EP 0 629 393 A (ICI AMERICAS) 21 December 1994 (1994-12-21) claims	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/16140

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/16140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9721838 A	19-06-1997	FR 2742164 A	13-06-1997
		AU 707137 B	01-07-1999
		AU 1100597 A	03-07-1997
		BR 9611990 A	30-03-1999
		CA 2238826 A	19-06-1997
		EP 0870064 A	14-10-1998
		HU 9903740 A	28-03-2000
		JP 2000501609 T	15-02-2000
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EP 119480 A	26-09-1984	DE 3306250 A	23-08-1984
		AT 40291 T	15-02-1989
		AU 561079 B	30-04-1987
		AU 2484384 A	30-08-1984
		CA 1220421 A	14-04-1987
		DE 3476337 D	02-03-1989
		ES 529959 D	16-04-1985
		ES 8504452 A	16-07-1985
		IL 71018 A	30-01-1987
		JP 1856746 C	07-07-1994
		JP 5073727 B	15-10-1993
		JP 59182290 A	17-10-1984
		PT 78146 A,B	01-03-1984
		US 4632843 A	30-12-1986
		ZA 8401287 A	31-10-1984
EP 314469 A	03-05-1989	JP 2018373 A	22-01-1990
		JP 1111798 A	28-04-1989
		JP 2602850 B	23-04-1997
		JP 1111799 A	28-04-1989
		JP 2650274 B	03-09-1997
		DE 3882011 A	29-07-1993
		DE 3882011 T	30-09-1993
		US 4990216 A	05-02-1991
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EP 435450 A	03-07-1991	US 5075291 A	24-12-1991
		AT 112676 T	15-10-1994
		AU 638074 B	17-06-1993
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		CA 2030670 A	23-05-1991
		DE 69013314 D	17-11-1994
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		ES 2065499 T	16-02-1995
		FI 905781 A,B,	23-05-1991
		JP 3209336 A	12-09-1991
		NO 905075 A	23-05-1991
		PT 95964 A	15-10-1991
		ZA 9009313 A	30-10-1991
GB 2160100 A	18-12-1985	AT 391806 B	10-12-1990
		AT 174885 A	15-06-1990
		AU 587190 B	10-08-1989
		AU 4348685 A	19-12-1985
		AU 4454389 A	22-03-1990
		BE 902626 A	10-12-1985
		CA 1264441 A	16-01-1990
		CY 1635 A	06-11-1992

IN ONAL SEARCH REPORT

Information on patent family members

al Application No
PCT/US 00/16140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2160100 A		DE 3520184 A	19-12-1985
		DK 264785 A	15-12-1985
		ES 544075 D	01-01-1987
		ES 8702141 A	16-03-1987
		FR 2565822 A	20-12-1985
		GB 2196851 A,B	11-05-1988
		GB 2196852 A,B	11-05-1988
		GR 851430 A	25-11-1985
		HK 25192 A	10-04-1992
		HU 40918 A,B	30-03-1987
		IE 58834 B	17-11-1993
		IT 1200080 B	05-01-1989
		JP 61010507 A	18-01-1986
		LU 85946 A	24-01-1986
		NL 8501578 A	02-01-1986
		NZ 212390 A	25-02-1992
		NZ 229059 A	25-02-1992
		NZ 233954 A	25-02-1992
		PT 80635 A,B	01-07-1985
		SE 504583 C	10-03-1997
		SE 8502950 A	15-12-1985
		SG 15492 G	16-04-1992
		ZA 8504520 A	25-02-1987
EP 629393 A	21-12-1994	AU 6455594 A	22-12-1994
		JP 7031408 A	03-02-1995
		NO 942256 A	19-12-1994

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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OCT 0 1 2001

Woodard, Emhardt, Naughton, Moriarty & McNett

PCT

To:

HENRY, Thomas Q.
WOODARD, EMHARDT, NAUGHTON,
MORIARTY & McNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.09.2001
Applicant's or agent's file reference 7040339LLY54	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/16140	12/06/2000	11/06/1999

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hutterer, G Tel.+49 89 2399-8066

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7040339LLY54		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/16140	12/06/2000	11/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/16		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	18.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Uhl, M Telephone No. +49 89 2399 8654

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/16140

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-70 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-14.

because:

☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-14 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Subject matter of claims 1-14 can not be evaluated because the feature "in a growth-specific orientation" is not clear, not even in the light of dependent claims nor in the description. The only reference in the description is p.11, 2nd paragraph. Here, it is described to refer to the fact that API molecules are "included primarily at certain faces of the crystal matrix ". Then, determination methods are described. However no technical teaching is given how to get there. The 4 examples do not give any guidance, because no indication at all is given, what controls this obscure parameter.

PATENT COOPERATION TREATY

RECEIVED
OCT 23 2000
Woodard, Emhardt, Naughton, Moriarty & McNett

PCT

From the INTERNATIONAL BUREAU

To:

HENRY, Thomas, Q.
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower
Suite 3700, 111 Monument Circle
Indianapolis, IN 46204
ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 09 October 2000 (09.10.00)	
Applicant's or agent's file reference 7040339LLY54	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/16140	International filing date (day/month/year) 12 June 2000 (12.06.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 11 June 1999 (11.06.99)
Applicant ELI LILLY AND COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
11 June 1999 (11.06.99)	60/138,912	US	19 July 2000 (19.07.00)

Th International Bureau f WIPO
34, ch min des Col mbettes
1211 Geneva 20, Switz rland

Facsimile No. (41-22) 740.14.35

Authorized officer

Carlos Naranjo

Telephone No. (41-22) 338.83.38

RECEIVED

MAR 2 1 2001

Woodard, Emhardt, Naughton, Moriarty & McNett

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

HENRY, Thomas, Q.
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower
Suite 3700, 111 Monument Circle
Indianapolis, IN 46204
ETATS-UNIS D'AMERIQUE

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

Date of mailing (day/month/year) 02 March 2001 (02.03.01)	
Applicant's or agent's file reference 7040339LLY54	**IMPORTANT INFORMATION**
International application No. PCT/US00/16140	**International filing date** (day/month/year) 12 June 2000 (12.06.00)
Priority date (day/month/year) 11 June 1999 (11.06.99)	
Applicant ELI LILLY AND COMPANY et al	

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
   National :AU,BG,CA,CN,CZ,DE,IL,JP,KP,KR,MN,NO,NZ,PL,RO,RU,SE,SK,US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
   National :AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,CH,CR,CU,DK,DM,DZ,EE,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MW,MX,
   MZ,PT,SD,SG,SI,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" **before the expiration of 30 months from the priority date** before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed **until 31 months from the priority date** for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

I. Britel

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

RECEIVED

JUN 07 2001

PCT Woodard, Emhardt, Naughton, Moriarty & McNett

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HENRY, Thomas Q.
WOODARD, EMHARDT, NAUGHTON,
MORIARTY & McNETT
Bank One Center/Tower, Suite 3700
111 Monument Circle
Indianapolis, Indiana 46204
ETATS-UNIS D'AMERIQUE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	01.06.2001
Applicant's or agent's file reference: 7040339LLY54	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/16140	12/06/2000	11/06/1999

International Patent Classification (IPC) or both national classification and IPC
A61K9/16

Applicant
ELI LILLY AND COMPANY et al.

ENTERED 9-1-01

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☐	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11/10/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Uhl, M

Formalities officer (incl. extension of time limits)
Hutterer, G
Telephone No. +49 89 2399 8066

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-70 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-14,

because:

   ☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-14 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

Re Item I
Basis of the opinion

Re Item II
Priority

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Subject matter of claims 1-14 can not be evaluated because the feature "in a growth-specific orientation" is not clear, not even in the light of dependent claims nor in the description. The only reference in the description is p.11, 2nd paragraph. Here, it is described to refer to the fact that API molecules are "included primarily at certain faces of the crystal matrix ". Then, determination methods are described. However no technical teaching is given how to get there. The 4 examples do not give any guidance, because no indication at all is given, what controls this obscure parameter.

REC'D 20 SEP 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
7040339LLY54		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/16140	12/06/2000	11/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/16		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2001	18.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Uhl, M Telephone No. +49 89 2399 8654

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/16140

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-70 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-14.

because:

☒ the said international application, or the said claims Nos. 1-14 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-14 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Subject matter of claims 1-14 can not be evaluated because the feature "in a growth-specific orientation" is not clear, not even in the light of dependent claims nor in the description. The only reference in the description is p.11, 2nd paragraph. Here, it is described to refer to the fact that API molecules are "included primarily at certain faces of the crystal matrix ". Then, determination methods are described. However no technical teaching is given how to get there. The 4 examples do not give any guidance, because no indication at all is given, what controls this obscure parameter.

INTERNATIONAL SEARCH REPORT

Int[redacted]al Application No
PCT/US 00/16140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 21838 A (ERIDANIA BEGHIN-SAY,FR) 19 June 1997 (1997-06-19) claims page 10, line 3 - line 18	1,7,10, 12-14
A	EP 0 119 480 A (BASF) 26 September 1984 (1984-09-26) claims	1-14
A	EP 0 314 469 A (FUJITSU LTD.,JP) 3 May 1989 (1989-05-03) claims	1-14
A	EP 0 435 450 A (ICI AMERICAS) 3 July 1991 (1991-07-03) cited in the application claims	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2000	13/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 160 100 A (SANDOZ) 18 December 1985 (1985-12-18) claims	1-14
A	EP 0 629 393 A (ICI AMERICAS) 21 December 1994 (1994-12-21) claims	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/16140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9721838 A	19-06-1997	FR 2742164 A	13-06-1997
		AU 707137 B	01-07-1999
		AU 1100597 A	03-07-1997
		BR 9611990 A	30-03-1999
		CA 2238826 A	19-06-1997
		EP 0870064 A	14-10-1998
		HU 9903740 A	28-03-2000
		JP 2000501609 T	15-02-2000
		US 6015466 A	18-01-2000
EP 119480 A	26-09-1984	DE 3306250 A	23-08-1984
		AT 40291 T	15-02-1989
		AU 561079 B	30-04-1987
		AU 2484384 A	30-08-1984
		CA 1220421 A	14-04-1987
		DE 3476337 D	02-03-1989
		ES 529959 D	16-04-1985
		ES 8504452 A	16-07-1985
		IL 71018 A	30-01-1987
		JP 1856746 C	07-07-1994
		JP 5073727 B	15-10-1993
		JP 59182290 A	17-10-1984
		PT 78146 A,B	01-03-1984
		US 4632843 A	30-12-1986
		ZA 8401287 A	31-10-1984
EP 314469 A	03-05-1989	JP 2018373 A	22-01-1990
		JP 1111798 A	28-04-1989
		JP 2602850 B	23-04-1997
		JP 1111799 A	28-04-1989
		JP 2650274 B	03-09-1997
		DE 3882011 A	29-07-1993
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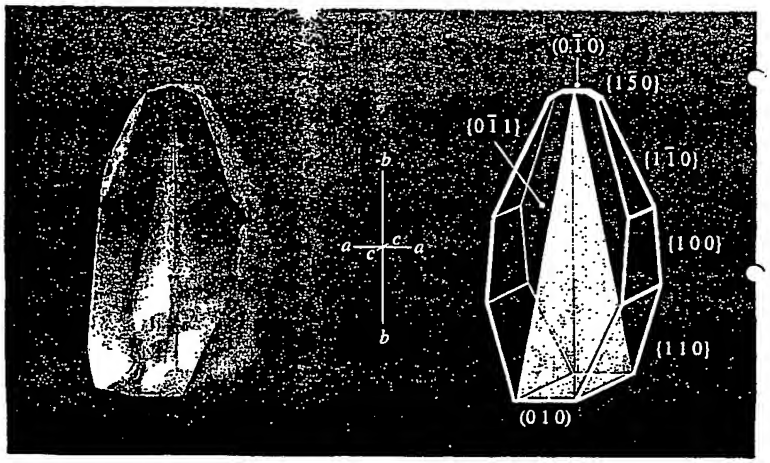
(54) Title: PHARMACEUTICAL MATERIALS AND METHODS FOR THEIR PREPARATION AND USE



(57) Abstract: Pharmaceutical compositions comprising crystals of a pharmaceutically-acceptable crystal lattice component, and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation. The crystals are prepared using components and methods which yield crystals having suitable purity and efficacy for use in administering the active pharmaceutical ingredients to a patient. The crystals are typically combined with adjuvants such as excipients, diluents or carriers, and are preferably formulated into tablets, capsules, suspensions, and other conventional forms containing predetermined amounts of the pharmaceuticals. Also provided are methods for preparing the crystals, and methods for storing and administering the active pharmaceutical ingredient either included within the crystals or upon reconstitution of the crystals to a solution.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PHARMACEUTICAL MATERIALS AND METHODS FOR THEIR PREPARATION AND USE

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to pharmaceutical formulations involving the inclusion of an active pharmaceutical ingredient ("API") in a pharmaceutically-acceptable single crystal matrix. More particularly, the crystals contain growth-sector specific, oriented inclusions of active pharmaceutical ingredients which are isolated. The active pharmaceutical ingredients have higher stability and shelf-life, and can be delivered in conventional dosage forms. This invention has general application to active pharmaceutical ingredients, and in one aspect has particular application to biopharmaceuticals. As used herein, the term "biopharmaceuticals" is used to refer to a subset of API's which are polymeric in nature, including for example, proteins, polypeptides, enzymes, immunoglobulins, polynucleic acids, and plasmids.

Description of the Prior Art:

There is a continuing need for pharmaceutical compositions which are capable of maintaining the quality and efficacy of the API during storage and delivery. The loss of potency of an API is a critical concern in assuring that viable, effective drugs are delivered to patients. It is similarly desirable to have formulations which do not require special packaging or handling. Further, it remains a constant goal to provide active pharmaceutical ingredients in a form which facilitates their use by the consumer, such as through convenient dosage forms. The present invention addresses these and other issues concerning pharmaceutical compositions and formulations.

Although not limited to biopharmaceuticals, the usefulness of the present invention is well exemplified with respect to biopharmaceuticals, many of which demonstrate the problems encountered in prior-art approaches. Ensuring long-term stability and maintaining activity of biopharmaceuticals is a prevalent concern. The chemical complexity and conformational fragility of protein drugs, for example, make them highly susceptible to both physical and chemical instabilities

and threaten their emergence into the marketplace. Denaturation, adsorption with container walls, aggregation, and precipitation can result from non-covalent interactions between a drug and its environment. Insulin, for instance, has been shown to adsorb onto the surfaces of glass and plastic containers, and to have interactions at air-water interfaces, leading to denaturation, aggregation and precipitation. For example, upon denaturation human growth hormone (HGH) forms dimers and higher molecular weight aggregates, and glucagon in solution has been shown to readily gel or aggregate when subjected to mechanical stress.

As a further example, researchers have distinguished nine major reaction mechanisms by which proteins degrade, including hydrolysis, imide formation, deamidation, isomerization, racemization, diketopiperazine formation, oxidation, disulfide exchange, and photodecomposition. The rates of these deleterious processes depend in large measure on the protein and its environment. The primary chemical degradation products of glucagon, for example, include oxidation of Met (27), deamidation of Gln (24), and acid-catalyzed hydrolysis at Asp (9), Asp (15) and Asp (21). HGH undergoes chemical decomposition via oxidation at Met (14) and deamidation at Asn (149).

A critical challenge of product development science in the pharmaceutical industry therefore has been devising formulations that maintain the stability of the active pharmaceutical ingredient over an acceptable shelf-life. This has been especially difficult to achieve for certain API's which are unstable in solution or with respect to many common formulation processes. Developing techniques for stabilization and storage looms as a great impediment to the pharmaceutical industry. Formulation scientists have consequently used a variety of techniques to enhance the stability of API's while maintaining other important product characteristics such as biocompatibility, absorption, pharmacokinetics, efficacy and excretion.

One technique used in formulating biopharmaceuticals has been lyophilization of the biopharmaceutical solution in the presence of excipients, buffers and/or bulking agents. However, even lyophilized preparations must typically be stored under refrigeration, a requirement which is neither technically

nor economically feasible in many markets and inhibits flexibility of patient use. There has therefore been a continuing demand for formulations of many biopharmaceuticals which would permit their storage at ambient temperatures. This would permit more rapid development of products, increasing flexibility in shipping, storing and carrying the drug products, and allowing introduction and use of such products in markets where refrigeration is too costly. Moreover, the increased stabilization of biopharmaceuticals would naturally improve the general use of the biopharmaceuticals where shelf life is an important consideration, whether or not refrigeration or other concerns are at issue.

The prior art use of excipients in the lyophilization of biopharmaceuticals has been directed away from inclusion of the biopharmaceuticals in single crystals in the manner of the present invention. It has been widely assumed that amorphous glasses are critical in the stabilization of biopharmaceuticals by such excipients in lyophilized form, and it has been suggested that the drug molecules must exist in amorphous regions between the crystalline domains. See, e.g., M. J. Pikal, "Freeze Drying of Proteins", to be published in Peptide and Protein Delivery, 2nd Ed., V. H. L. Lee, Marcel Dekker, Preprint, 1995. Implicit in this reasoning is the conclusion that the biopharmaceuticals could not exist as guests within single crystals.

In the process of lyophilization, typically an aqueous solution containing a biopharmaceutical with a limited amount of excipient(s) is frozen and then dried under vacuum to produce solids of sufficient stability for storage and distribution. Excipients are added to prevent blow out of the product, to provide stability during lyophilization and/or dissolution, and to enhance compatibility for parenteral use. Various excipients used with lyophilization have included salts, metal ions, polyalcohols, surfactants, reducing agents, chelating agents, other proteins, amino acids, fatty acids, and phospholipids. The more frequently used excipients include mannitol, alanine, glycine, sorbitol, lactose, arginine, and maltose. The results obtained with such excipients, however, have usually been inconsistent. Most lyophilized biopharmaceuticals are amorphous powders that have no specific structure, and as a result, the amount and location of the incorporated biopharmaceutical varies widely for the product particles. Also, they are typically

readily dissolved, rendering them unsuitable for use as a sustained-release material. Further, there is no isolation of the pharmaceutical molecules from the environment or one another, leaving them susceptible to degradation by various mechanisms. Studies have shown that lyophilization of excipients can typically damage proteins rather than protect them. See, e.g., J. F. Carpenter, J. H. Crowe, "Infrared spectroscopic studies of the interaction of carbohydrates with dried proteins", Biochemistry 1989, 28, 3916-3922; J. F. Carpenter, S. Prestrelski, T. Arakawa, "Separation of freezing- and drying-induced denaturation of lyophilized proteins by stress-specific stabilization: I. Enzyme activity and calorimetric studies," Arch. Biochem. Biophys. 1993, 303, 456-464. K. Izutsu, S. Yoshioka, Y. Takeda, "The effects of additives on the stability of freeze-dried β-galactosidase stored at elevated temperatures", Int. J. Pharm. 1991, 71, 137-146. K. Izutsu, S. Yoshioka, T. Teroa, "Decreased protein-stabilizing effects of cryoprotectants due to crystallization", Pharm. Res. 1993, 10, 1232-1237.

Crystallized pharmaceuticals have been used in some instances, but there have been inherent limitations. Some API's , e.g. insulin, can be crystallized themselves, and are useful in that form for administration to patients. However, the majority of biopharmaceuticals either do not crystallize or the crystallization is very difficult, particularly on a commercial scale. Further, crystallization procedures are limited to the use of pharmaceutically-acceptable ingredients and process conditions that do not adversely affect the active pharmaceutical ingredient, thus further constraining the ability to obtain desired microcrystalline suspensions.

The fact that macromolecules are routinely isolated in sub-millimolar concentrations in a variety of crystals is known. See, e.g., K. Strupat, M. Karas, F. Hillenkamp, Int. J. Mass Spec. Ion Proc., 111, 89-102, 1991. Also, certain aromatic acids have been employed as hosts for biopolymer guests in crystals for use in matrix-assisted laser desorption ionization (MALDI) mass spectrometry, but not for the purposes of the present invention. See, Review by F. Hillenkamp, M. Karas, R.C. Beavis, B.T. Chait, Anal. Chem, 63, 1193A-1203A; S. Borman, Chem. Eng. News, 23-25, June 19, 1995. However, crystallization conditions in

these studies were optimized for characterization of the incorporated biopolymers. There were no investigations into optimizations that would be relevant to pharmaceutical preparations or operations such as homogeneity of the concentration of the inclusions, process scale-up, process robustness, chemical and physical stability of the preparations, suspendability in biocompatible solutions, preservative requirements and compatibility, container/closure system compatibility, and pharmacokinetic profiles.

The difficulty in obtaining suitable single crystals of some biopolymers has encouraged structural chemists to partially orient such molecules with electric, magnetic, or flow fields, by dissolution in liquid crystals or stretched gels, and as monolayers. In a similar effort, the isolation of biopolymers in a single crystal matrix has recently been studied in an effort to use such crystals for structural analysis of the biopolymers. Such isolation technique is described in "Single Crystal Matrix Isolation of Biopolymers," J. Chmielewski, J.J. Lewis, S. Lovell, R. Zutshi, P. Savickas, C.A. Mitchell, J.A. Subramony, and B. Kahr, J. Am. Chem. Soc. 1997, 119, 10565-10566. However, this article simply demonstrates that certain biopolymers are oriented by the host lattice, and the article suggests the use of such crystals for analyzing spectral anisotropies in biological molecules which could not otherwise be crystallized. This article does not discuss or suggest the use of this technique for enhancement of stability or sustained release of pharmaceuticals, or their administration to patients. Further, the proteins studied were not of pharmaceutical interest, the crystal materials described in this article, namely phthalic acid, gentisic acid and sinapic acid, were not selected or evaluated for biocompatibility, and the crystal sizes were not optimized for particular routes of administration. Therefore, the produced crystals with included biopolymers would not be suitable for administration to patients.

Other prior art procedures have required the use of polymers that are difficult to prepare, require harsh preparation conditions that can be harmful to the API's, and yield inconsistent results. For example, United States Patent No. 5,075,291 describes a process for preparing a uniformly-dispersed, pharmaceutically-active material in a crystalline sugar alcohol matrix. However,

this process requires the addition of the API into a molten sugar alcohol with considerable mechanical agitation. Many API's and virtually all biopharmaceuticals would not be stable in the extreme temperature of 110°C and the physical stresses of a high-shear vortex mixer used for agitation. The present invention does not require these extremes of temperature and physical agitation. Also, the process of the present invention slowly includes the API into the growing crystal lattice in specific growth sectors, instead of homogeneous mixing and entrapping of the active pharmaceutical ingredient in a viscous melt.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to pharmaceutical compositions comprising single crystals of a pharmaceutically-acceptable crystal lattice component, and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation. The crystals are prepared using components and methods which yield crystals having suitable purity and efficacy for use in administering the API's to a patient. The crystals may be coated or combined with adjuvants such as excipients, diluents or carriers, and are preferably formulated into tablets, capsules, suspensions, and other conventional forms containing dosage amounts of the API's. Alternatively, the crystals are prepared as depot formulations which may be administered, as by subcutaneous injection or implantation, to provide a long-term payout or sustained release of the active pharmaceutical ingredient. The present invention further provides methods for preparing the crystals and for storing and administering the active pharmaceutical ingredient either in crystal form or upon reconstitution to a solution.

Accordingly, it is an object of the present invention to provide single crystals which include API's in a growth-sector specific orientation. It is a feature of the invention that the API's are included at predictable, uniform concentrations that permit use of the crystals in formulating dosage amounts of the API's.

Another object of the present invention is to provide compositions comprising API's included in single crystals to provide improved stability and shelf-life. The active pharmaceutical ingredients may therefore be stored for extended periods of time prior to use either as crystals or as reconstituted solutions.

It is a further object of the present invention to provide single crystals with included API's to provide quick, delayed-release or sustained-release formulations for flexibility in pharmacokinetic profiles in delivery of the API's to patients.

Another object of the present invention is to provide pharmaceutical delivery units including an amount of single crystals sufficient to provide a dosage amount of the included active pharmaceutical ingredient. Alternatively, the pharmaceutical delivery units include a quantity of crystals sufficient to provide a

prolonged payout of the active pharmaceutical ingredient. The crystals may be coated or uncoated, and may be combined with various pharmaceutical adjuvants including excipients, diluents and carriers.

A further object of the present invention is to provide methods for preparing compositions comprising single crystals with growth-sector specific inclusions of API's.

It is another object of the present invention to provide methods for the storage and administration of API's utilizing inclusion of the API's within single crystals.

Other objects, features, and advantages of the present invention will be apparent to those skilled in the art from the following description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photomicrograph illustrating fluorescence of a single crystal of green fluorescent protein in α-lactose monohydrate (1.8 (h) x 0.8 (w) x 0.5 (d) mm^3) with an idealized representation of habit. The sides of the crystal in the photomicrograph are bright due to internal reflection.

Figure 2 is a graph of the fluorescence decay of the green fluorescent protein at 333°K in several environments: mixed crystal in α-lactose monohydrate (triangle), saturated lactose solution (square), and lyophilized α-lactose monohydrate (diamond).

DESCRIPTION OF THE PREFERRED EMBODIMENT

For the purposes of promoting an understanding of the present invention, reference will now be made to the embodiments described hereafter. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such modifications and applications of the principles of the invention as described herein being contemplated as would normally occur to one skilled in the art to which the invention relates.

The present invention utilizes single-crystal matrix inclusion of active pharmaceutical ingredients ("API's") to achieve advantageous storage and delivery of the API's. This invention has application to a wide range of API's to provide enhanced stability and/or delivery of the active pharmaceutical ingredients. For some applications, such as for many biopharmaceuticals, the invention is particularly advantageous in providing greater stability over time and in providing alternative delivery and sustained release formulations to patients .

The small molecule host crystals comprise a crystal lattice component which includes the API's in an oriented, growth-sector specific manner. The crystals and included API's are prepared to be pharmaceutically acceptable and pure, thereby being useful for administration to patients to be treated with the API's. As used herein, the term "pharmaceutically-acceptable" refers to sufficient quality to meet regulatory and compendial requirements for administration to humans and/or animals. The crystals provide a regular, predictable inclusion of the guest active pharmaceutical ingredient, and the crystals can consequently be used for obtaining a predetermined amount of the active pharmaceutical ingredient for delivery to a patient. In one aspect, the host crystal gradually dissolves upon contact with body tissue or fluids, and is therefore useful as a system for delivery of the active pharmaceutical ingredient into the body. Alternatively, the crystals and included active pharmaceutical ingredient may be reconstituted into a solution for administration to a patient.

The active pharmaceutical ingredient molecules are generally isolated from one another and are insulated from the environment by the host crystal. This leads to reduced susceptibility of the API to degradation, and therefore enhanced

stability and shelf-life. Also, the use of appropriate host crystal compounds, or selected dosage forms, permits the design of quick, delayed, or sustained-release formulations for delivery of the active pharmaceutical ingredient. Sustained-release formulations are particularly advantageous for treatment of chronic conditions as they provide a consistent amount of drug delivery over a long period of time to improve ease of use and patient compliance in administering the API.

The crystals preferentially incorporate the active pharmaceutical ingredient on certain faces, thereby providing a growth-sector specific inclusion and orientation to the API's. As used herein, the term "growth-sector specific inclusion and orientation," and equivalent terminology, refers to the fact that the API molecules are included primarily at certain faces of the crystal matrix. The growth-sector specific inclusion and orientation can be determined by one skilled in the art, as demonstrated in the examples herein, by fluorescence microscopy and anisotropy measurements, single crystal desorption mass spectrometry, and autoradiography of ^{14}C-labeled material. In one embodiment, at least about 0.001% (on weight/weight (w/w) basis) of the pharmaceutical is included within specific faces of the crystal matrix, and in another embodiment at least about 0.1% (w/w) and up to about 10%. The crystal parameters, including the particular crystal lattice component for a given API, the concentration of API, the use of crystal adjuvants, and the crystallization conditions, are selected to achieve the growth-sector specific inclusion and orientation of the API within the crystals.

The method of the present invention broadly involves the including of the active pharmaceutical ingredient into the single crystal matrix formed from a pharmaceutically-acceptable crystal lattice component. As used herein, the term "included" in the crystals refers to the active pharmaceutical ingredient being chemically adsorbed within the crystal lattice as the crystal is formed. This inclusion of the active pharmaceutical ingredient molecules is distinguished from crystallization of the API molecules with one another, and from simple and random entrapment of the API molecules by the formed crystal. The crystal product of the present invention is ordered, in contrast to the amorphous material produced by other approaches. The API is incorporated in the crystal in relation to its degree of

affinity for the crystal lattice molecules. The crystal lattice component is therefore selected to be both chemically and physically compatible with the API such that the API is received by the crystal during formation, and remains stable and efficacious while within the crystal and upon release therefrom.

In a typical approach, the including of the active pharmaceutical ingredient involves combining the crystal lattice component, the active pharmaceutical ingredient and a pharmaceutically-acceptable adjuvant in a liquid state. The crystal lattice component is then crystallized under pharmaceutically-acceptable conditions to form the inventive crystals. For example, one method uses spiking of the API into a saturated or supersaturated solution of the crystal lattice component in a suitable organic and/or aqueous solvent system. Alternately, the saturated or supersaturated solution of the crystal lattice component may be spiked into the API solution. Other components may also be added to the solution, including compounds which facilitate or modify crystal growth or which are desired for incorporation in the final formulation. The solution may be seeded using any of a variety of conventional techniques.

In one approach, the solution is allowed to evaporate and/or equilibrate to cooler conditions for growth of the crystals. The crystals are then grown as the solvent is slowly evaporated away and/or the solution is cooled, with the evaporation and temperature gradient conditions being selected dependent on such factors as the solvent system and the desired crystal size. The crystals containing the active pharmaceutical ingredient are harvested from the remaining solution and are preferably washed to remove surface contamination. This procedure yields crystals which include the active pharmaceutical ingredient at a predictable concentration and facial orientation.

In accordance with the present invention, crystals are grown under pharmaceutically-acceptable conditions. As used herein, the term "pharmaceutically-acceptable conditions" refers to the use of crystal and API compounds which are pharmaceutically-pure, and for which such pharmaceutical purity is maintained in the final crystals. The crystal and API compounds are pharmaceutically pure, or have pharmaceutical purity, if they are of sufficient

purity to be suitable for administration under applicable FDA or other administrative regulations regarding purity. The term pharmaceutically-acceptable conditions further refers to the use of crystallization conditions through which the API compounds retain pharmaceutical efficacy in the final crystals and upon subsequent administration to patients.

The present invention readily allows the inclusion of API's by affinity with the small host molecules in the growing crystal lattice. This overcomes many of the limitations associated with previous approaches. The processing involved with preparing the present crystals does not expose the API's to harsh conditions, thereby substantially reducing or avoiding the possible degradation or disruption of the structural aspects of the API which could occur with prior art techniques. The inventive crystals have an added advantage in that they do not interfere with normal analytical methodologies used for characterizing the pharmaceutical product. The small host molecules can be easily separated on the basis of molecular size, which is not the case for prior art techniques which use polymers that interfere with analytical methodologies.

The API molecules are incorporated into the host crystals typically at rates of at least about 0.001% (w/w), preferably at least about 0.1%, and more preferably about 1% to about 10% (w/w). Alternatively, the API molecules are included at rates of at least about 0.01%, and as much as at least about 1% (w/w). The limited molar concentration of the active pharmaceutical ingredient in the host crystals means that the active pharmaceutical ingredient molecules are generally isolated from one another in the crystals. Isolation of the API molecules is particularly advantageous for those molecules, such as certain biopharmaceuticals, which could otherwise react with one another (e.g., by polymerization) or the surrounding environment. The degree of isolation can be verified by those skilled in the art using atomic force microscopy or reaction fluorescence energy techniques. The present invention has a particular application to guest-host systems in which the guest API molecules are reactive with one another, but in which these molecules are sufficiently isolated from one another in the crystals as to substantially prevent such interaction. Consequently, the invention provides containment of the API

molecules in the solid state crystals and provides for the API to be comformationally stable.

The method preferably involves preparing a mixture of crystals of substantially uniform size. This may include processing of the harvested crystals, such as by grinding or milling, to reduce the crystals to a substantially uniform size. Greater uniformity can be achieved by sorting the processed crystals, such as by sieving. A preferred method further includes obtaining crystals which have a substantially uniform concentration of pharmaceuticals, for example, about 1% (w/w) of pharmaceuticals, that do not vary between crystals by more than 10 percent.

The method of the present invention may further include formulating the crystals into pharmaceutical preparations. For example, the collected crystals may optionally be coated with a suitable composition. Coated or uncoated crystals may be blended with one or more pharmaceutically-acceptable adjuvants, such as excipients, diluents, carriers or mixtures thereof. The blended crystals and adjuvant(s) are then formulated into pharmaceutical delivery units. In one embodiment, each unit includes a predetermined amount of the pharmaceutical. Alternatively, the crystals are combined in a delivery unit intended to deliver multiple or sustained dosing of the API over a period of time, such as by subcutaneous implantation of the delivery unit. A further aspect of the method of the present invention involves reconstituting the crystals to liquid form. In accordance with this method, the harvested crystals are dissolved in a suitable diluent for the crystal lattice component. The dissolution of the crystals releases the API from the crystals. The resulting solution may include other adjuvants, such as excipients, diluents or carriers, and the mixture is formulated under conventional procedures to desired delivery forms. In a particular aspect of the present invention, the crystals are used to store the pharmaceutical for a period of time, such as at least one month, or at least one year, and the crystals are subsequently dissolved to use the active pharmaceutical ingredient.

The present invention involves the use of any of a wide variety of pharmaceutically-acceptable host crystal systems that can incorporate API's in a

growing crystal lattice. The crystal lattice component is selected to be compatible with the guest API, and to be suited to the use of the resulting formulation for storage and administration. Selection of the crystal lattice component will involve consideration of such factors as affinity for the API, crystal size distribution and morphology, and desired pharmaceutical concentration and delivery rate, as well as other factors well known in the art of pharmaceutical delivery systems. The crystal systems must consistently incorporate the guest active pharmaceutical ingredient in terms of concentration and placement within the crystal lattice. The crystals also must grow under conditions which will not degrade or otherwise adversely affect the viability of the active pharmaceutical ingredient.

Preferred host crystal materials are those that have a high affinity for the included API. It appears that the oriented inclusion of the API's is related to the affinity between the crystal lattice component and the API. The affinity between these materials is therefore important in obtaining the desired inclusion of the API's, and also permits control of the inclusion based upon this affinity. For example, the concentration of the pharmaceutical in a crystal can be controlled by selecting the host component to have an affinity for the API which yields the desired inclusion rate. Also, mixtures of host materials, or of host materials and other excipients, can be used to provide an affinity yielding the desired inclusion level. In one aspect of the present invention, the API's are incorporated at levels of at least about 0.001% (w/w of guest:host), more preferably at least about 0.1% (w/w).

The preferred host crystal materials will also be very stable and readily crystallizable, and will maintain their "order" or crystal morphology when including a guest molecule, particularly large biomolecules. The use of particular host crystal components will also depend on such factors as how small or large the crystals can be produced and how readily they dissolve. For various routes of administration, it is desirable to have very small crystals (e.g., pulmonary), moderately sized crystals (e.g., injectable), or very large crystals (e.g., implantation and long term payout). The useful crystal sizes will therefore vary accordingly,

ranging from submicron to millimeter sizes. In one aspect of the present invention, the preferred crystals are in the order of 5-100 microns in size.

The useful host crystal systems are therefore diverse, and include various small molecule crystal systems which meet the desired criteria. Examples of pharmaceutically-acceptable crystal lattice components include sugars, polyhydroxy alcohols, single and polyamino acids, vitamins, salts, metals, preservatives, aromatic compounds especially aromatic acids, purified natural products, and polymers. Preferred crystal lattice components include, for example, sucrose, lactose, trehalose, maltose, galactose, sorbose, mannitol, lactitol, sorbitol, glycine, alanine, lysine, arginine, ascorbic acid, nicotinamide, thiamine, adenine, pyridoxine hydrochloride, caffeic acid, vanillic acid, ferulic acid, benzoate, sorbate, methyl paraben, sodium ascorbate, sodium saccharin, and potassium citrate. Also, compatible mixtures of these materials are also useful, and can be selected to obtain the desired rate of inclusion of the pharmaceutical, or to achieve desired characteristics, such as dissolution rate and pharmacokinetic profile, for the product crystals.

The crystal lattice components are selected to achieve the desired pharmacokinetics for the final crystals. As pertains to the present invention, the term "pharmacokinetics" is used to refer to the profile of the delivery of active pharmaceutical ingredient from the crystals into the circulatory system. This will depend primarily on the concentration of the active pharmaceutical ingredient in the crystals, as well as parameters of the active pharmaceutical ingredient itself. While given crystal lattice components will have associated inclusion and dissolution characteristics, these can be modified by including other crystal lattice components, other API's, or a variety of excipients. Thus, single crystals having two different, co-crystallized lattice components will typically be characterized by pharmacokinetic profiles different from crystals prepared with either of the crystal lattice components alone. Similarly, including excipients or other API's will provide altered rates of inclusion or dissolution for the resulting crystals, providing an associated modification in the pharmacokinetic profile for the resulting crystals.

In a related aspect, the present invention involves the use of mixtures of crystals having different pharmacokinetics in order to achieve desired payout profiles. For example, a pharmaceutical product can be obtained by combining two different types of crystals, one type of crystal using a first crystal lattice component characterized by a first pharmacokinetic profile, and the second type of crystal using a second crystal lattice component characterized by a second pharmacokinetic profile. The mixture of crystals will give a payout of API that is different from either of the individual payouts for the two crystal types.

The included API's are similarly diverse, limited simply by the requirements of compatibility with the host crystal and the crystal growth conditions. The active pharmaceutical ingredient cannot be unacceptably degraded or otherwise adversely affected by the conditions under which the crystals are formed. Also, the active pharmaceutical ingredient should remain stable for an extended period of time while included within the host crystal, and pharmaceutically efficacious upon release from the crystal.

Given the foregoing criteria, examples of API's useful in accordance with the present include: antibiotics (such as dirithryomycin, loracarbef, tilmicosin, vancomycin, tylosin, monensin), fluoxetine, raloxifene, olanzapine, and nizatidine. A more complete list of API's useful in accordancw with the present invention would include those identified in the following Table A.

TABLE A

Marketed Recombinant Protein Products

Tissue Plasminogen Activator, T-PA

- **Product name:** Activase (Generic name: Altepase)
- **Produced by:** Genentech
- **Indication:** Human use, Acute myocardial infarction
- **Date of approval:** Nov 87, Patent expires on Dec 2000.
- **Formulation:** Intravenous injection. Lyophilized powder which is reconstituted with sterile water (supplied) to 1 mg/mL and results in a final pH of 7.3. Can not be reconstituted with preserved water due to precipitation. The 1 mg/mL solution can be diluted 1:1 with 0.9% NaCl or D5W and help for 8 hours at room temperature. TPA is incapable with preservatives.

Ingredients	100 mg vial	50 mg vial	20 mg vial
T-PA	100 mg	50 mg	20 mg
L-Arginine	3.5 g	1.7g	0.7g
Phosphoric acid	1g	0.5g	0.2g
Polysorbate 80	<11 mg	<4 mg	<1.6 mg
Vacuum	No	Yes	Yes

- **Expression System:** Mammalian cell line (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 527 amino acids, sequence from human melanoma cell line, activity of 580,000 IU/mg,
- **Additional Information:** Sales > $100 million. Cost of therapy $2,750 (100 mg).

Interferon Gamma-1b

- **Product name:** Actimmune
- **Produced by:** Genentech
- **Indication:** Human use, chronic granulomatous disease
- **Date of approval:** Dec 1990
- **Formulation:** Single dose solution formulation (0.5 mL), subcutaneous injection. Each 0.5 mL contains 100µg interferon gamma-1b, 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg polysorbate-20 in sterile water.
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:** Single chain; Human sequence, 140 amino acids, 16,465 molecular weight, non-covalent dimeric form in solution, activity of 30 million units/mg.
- **Additional Information:** 14% injection site irritation vs. 2% in placebo. Cost $140 for 50µg.

Interferon alfa-n3 (natural source, not recombinant)

- **Product name:** Alferon N
- **Produced by:** Interferon Science (New Brunswick, NJ)
- **Indication:** Human use, Genital Warts
- **Date of approval:** Jun 90
- **Formulation:** Preserved solution formulation (each mL contains 5 million IU of interferon alfa-n3 in phosphate buffered saline containing 3.3 mg phenol and 1 mg human albumin). Injected intralesional twice weekly for up to 8 weeks (50µL injected into each wart, 500µL total dose per treatment).
- **Expression System:** Natural source - human leukocytes which are exposed to an avian virus in order to produce interferon.
- **Refolding Conditions:** None
- **Structure:** Approximately 166 amino acids with a molecular weight ranging from 16 to 27 kDa, specific activity of 20,000 IU/mg or greater.
- **Additional Informati n:** Cost $142 per mL.

Beta Interferon 1a

- **Product name:** Avonex
- **Produced by:** Biogen (Cambridge, MA)
- **Indication:** Human use, Multiple Sclerosis
- **Date of approval:** May 95

TABLE A

- **Formulation:** Lyophilized powder (stored refrigerated or at 25°C for < 30 days) which is reconstituted with sterile water (supplied, 1.1mL) to 30 µg/mL beta interferon 1a, 15 mg/mL human albumin, 5.8 mg/ml NaCl, 5.7 mg/ml dibasic Na phosphate, 1.2 mg/ml monobasic sodium phosphate, and has a pH of approximately 7.3 (recon solution is stable for 6 hours at refrigerated temperatures). Weekly intramuscular injection by patient or doctor (dosed for 1-2 years in clinical trials).
- **Expression System:** Mammalian cells (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein (single N-linked complex carbohydrate), 166 amino acids with a predicted molecular weight of 22,500 daltons, human sequence, has a specific activity of 200 million units per mg protein.
- **Additional Information:** Cost $180 per vial (33µg)

Interferon beta-1b

- **Product name:** Betaseron
- **Produced by:** Berlex Laboratories (Wayne, NJ and Chiron, Emeryville, CA)
- **Indication:** Human use, Multiple Sclerosis
- **Date of approval:** July 93.
- **Formulation:** Lyophilized product (stored refrigerated) which is reconstituted with 0.54% NaCl (supplied) to 0.25 mg/mL interferon beta-1b, 12.5 mg/mL human albumin, 12.5 mg/ml dextrose, and has a pH of approximately 7.3 (recon solution is stable for 3 hours). Injected subcutaneously every other day (chronic use).
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Structure:** 165 amino acids with an approximate molecular weight of 18,500 daltons, human sequence but with a serine or cysteine substitution at residue 17. Recombinant form does not contain the carbohydrate moiety found in the natural material. Has a specific activity of 32 million units per mg protein.
- **Additional Information:** Sales > $500 million. Cost of therapy is $13,140 (based on 0.25 mg/injection, dose every other day for 1 year; equals 46 mg protein).

Interferon alfa-2b

- **Product name:** Intron A
- **Produced by:** Schering-Plough (Madison, NJ)
- **Indication:** Human use, Hairy cell leukemia, genital warts, Hepatitis, Melanoma, Kaposi's sarcoma
- **Date of approval:** June 86
- **Formulation:** Comes in a lyophilized and a solution formulation. The lyophilized formulations when reconstituted with 0.9% benzyl alcohol (supplied) contains either 0.015, 0.025, 0.05, 0.90, or 0.125 mg/mL Interferon alfa-2b, 20 mg/ml glycine, 2.3 mg/ml sodium phosphate dibasic, 0.55 mg/ml sodium phosphate monobasic, and 1 mg/ml human albumin. The solution formulations contain either 0.05, 0.114, or 0.125 mg/mL Interferon alfa-2b, 20 mg/ml glycine, 2.3 mg/ml sodium phosphate dibasic, 0.55 mg/ml sodium phosphate monobasic, 1 mg/ml human albumin, 1.2 mg/mL methylparaben, and 0.12 mg/ml propylparaben. These formulations be injected intramuscular, subcutaneous, or intralesional. All formulations and reconstituted products are stored at refrigerated temperatures.
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Structure:** Water soluble protein a molecular weight of 19,271 daltons. The Interferon alfa-2b gene is derived from human leukocytes.
- **Additional Information:** Sales > $500 Million. Cost of therapy is $16,445 (5 million units every day for 1 year, this is equal to 9 mg protein). Specific activity is 200 million units per mg protein

Interferon alfa-2a

- **Product name:** Roferon-A
- **Produced by:** Hoffmann-La Roche (Nutley, NJ)
- **Indication:** Human use, Hairy cell leukemia, Kaposi's sarcoma, myelogenous leukemia
- **Date of appr val:** June 1986
- **Formulation:** Multi-use and lyophilized formulation indented for intramuscular or subcutaneous administration. Multi-use formulation contains either 0.015, 0.045, 0.090, 0.18 mg/mL Interferon alfa-2a, 9 mg/ml NaCl, 5 mg/ml human albumin, and 3 mg/ml phenol. The lyophilized formulation reconstituted with 3 mL of supplied diluent (6 mg/ml NaCl, 3.3 mg/ml phenol) consists of 0.03 mg/ml Interferon alfa-2a, 9 mg/ml NaCl, 1.67 mg/ml human albumin, and 3.3 mg/ml phenol.
- **Expressi n System:** *E. coli* (tetracycline promoter).

TABLE A

- **Refolding C nditions:**
- **Structure:** Protein of 165 amino acids having a molecular weight of 19,000 daltons
- **Additional Information:** Cost of therapy is $59,200 (28mg protein over 1 year). Specific activity is 200 million international units per mg protein.

Human Growth Hormone (Somatropin)
- Product name: BioTropin
- Produced by: Bio-Technology General (Iselin, NJ)
- Indication: Human use, Growth Deficiency
- Date of approval: May 95
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)
- **Product name:** Genotropin
- **Produced by:** Pharmacia and Upjohn (Kalamazoo, MI)
- **Indication:** Human use, Growth Deficiency
- **Date of approval:** Aug 95
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)
- **Product name:** Humatrope
- **Produced by:** Eli Lilly (Indianapolis, IN)
- **Indication:** Human use, Growth Deficiency
- **Date of approval:** March 87
- **Formulation:** Lyophilized product which is reconstituted with sterile water containing 0.3% m-cresol, 1.7% glycerin (supplied) to 2 mg/mL hGH and has a final pH of approximately 7.5, subcutaneous or intramuscular administration. Each 5 mg lyophilized vial contains 5 mg hGH, 25 mg mannitol, 1.13 mg dibasic sodium phosphate, and 5 mg glycine.
- **Expression System:** *E. coli.*
- **Refolding Conditions:**
- **Structure:** 191 amino acids, molecular weight of 22,125 daltons, sequence is identical to human pituitary-derived material.
- **Additional Information:** Cost $210 per 5 mg hGH.

Human Growth Hormone (Somatropin)
- Product name: Norditropin
- Produced by: Novo Nordisk (Princeton, NJ)
- Indication: Human use, Growth Deficiency
- Date of approval: July 91
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional M difications:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)
- Product name: Nutropin and Nutropin AQ
- Produced by: Genentech
- Indication: Human use, Growth Deficiency

TABLE A

- **Date of approval:** March 1994
- **Formulation:** Lyophilized product which is reconstituted with bacteriostatic water (0.9% benzyl alcohol, supplied) to 5 mg/mL hGH and has a final pH of approximately 7.4, subcutaneous or intramuscular administration. Each 5 mg lyophilized vial contains 5 mg hGH, 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg monobasic and 1.3 mg dibasic), and 1.7 mg glycine.
- **Expression System:** *E. coli*, expressed with a leading secretion signal precursor which directs the protein to the plasma membrane of the cell where the sequence is removed and the native protein is secreted into the periplasm so that the protein if folded appropriately as it is synthesized
- **Refolding Conditions:** None, expressed folded in E. coli.
- **Structure:** 191 amino acids, molecular weight of 22,125 daltons, sequence is identical to human pituitary-derived material.
- **Additional Information:** Cost $420 per 10 mg hGH.

β-Glucocerebrosidase (imiglucerase)

(β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C.3.2.1.45)

- **Product name:** Cerezyme
- **Produced by:** Genzyme (Cambridge, MA)
- **Indication:** Human use, Gaucher's disease
- **Date of approval:** May 94
- **Formulation:** Lyophilized product (212 units glucocerebrosidase, 155 mg mannitol, 70 mg sodium citrate, and 0.53 mg polysorbate-80; stored refrigerated) is reconstituted with 5.1 mL of sterile water, final pH is approximately 6.1. The reconstituted material is combined with 100 to 200 mL of 0.9% NaCl and administered intravenously.
- **Expression System:** Mammalian cell culture (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites, molecular weight is 60,430 daltons. Recombinant protein differs from human placental glucocerebrosidase by a arginine substituted for histidine at position 495 and the glycosylation sites have been modified to terminate in mannose sugars (which are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease).
- **Additional Information:** Orphan Drug, sales > $100 million, Cost of therapy is $351,130 (1 year).

Hepatitis B Surface Antigen

- **Product name:** Engerix-B
- **Produced by:** SmithKline Beechman (Philadelphia, PA)
- **Indication:** Human use, Hepatitis B
- **Date of approval:** Sept 89
- **Formulation:** Suspension (20μg/mL hepatitis B surface antigen adsorbed onto 0.5 mg aluminum, 1:20,000 thimerosal, 9 mg/ml NaCl, 1.7 mg/ml sodium phosphates). Intramuscular administration.
- **Expression System:** A portion of the hepatitis B virus gene, coding for hepatitis B surface antigen, in cloned into yeast (*Saccharomyces cerevisiae*)
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:** Formulation contains no more than 5% yeast proteins.

Hepatitis B Surface Antigen

- **Product name:** Recombivax HB
- **Produced by:** Merck (Whithouse Station, NJ)
- **Indication:** Human use, Hepatitis B prevention
- **Date of approval:** July 1986
- **Formulation:** Suspension (10μg/ml hepatitis B surface antigen adsorbed onto 0.5 mg aluminum, 1:20,000 thimerosal). Intramuscular administration.
- **Expression System:** A portion of the hepatitis B virus gene, coding for hepatitis B surface antigen, in cloned into yeast (*Saccharomyces cerevisiae*)
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:** Formulation contains no more than 1% yeast proteins.

Erythropoietin (rEPO)

TABLE A

- **Product name:** Epogen or Epoetin alfa (Also sold under the name Procrit by Ortho Biotech but manufactured by Amgen)
- **Produced by:** Amgen (Thousand Oaks, CA)
- **Indication:** Human use, Anemia
- **Date of approval:** June 89, Patent expires in 2004 (December).
- **Formulation:** Two solution formulations, single dose and multi-dose. Single-dose is preservative free and each mL contains 2000, 3000, 4000, or 10000 units Epogen, 2.5 mg human albumin, 5.8 mg sodium citrate, 5.8 mg NaCl, and 0.06 mg citric acid in water for injection, pH 6.9 +/- 0.3. The preserved multi-dose product contains 10,000 units Epogen, 2.5 mg human albumin, 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid and 1% benzyl alcohol per mL of solution, pH is 6.1 +/- 0.3. Both solutions are stored refrigerated.
- **Expression System:** Mammalian cell
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 165 amino acids having a molecular weight of 30,400 daltons, sequence identical to that of the human protein.
- **Additional Information:** Sales > $500 million, Cost $120 for 10,000 units.

Human Insulin

- Product name: Humulin
- Produced by: Eli Lilly (Indianapolis, IN)
- Indication: Human use, Diabetes
- Date of approval: Oct 82
- **Formulation:**
- **Expression System:** *E. Coli*
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:** Sales > $500 Million.

Human Insulin

- Product name: Novolin
- Produced by: Novo Nordisk (Princeton, NJ)
- Indication: Human use, Diabetes
- Date of approval: July 91
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Translational Modifications:**
- **Structure:**
- **Additional Information:**

LysPro Human Insulin

- Product name: Humulog
- Produced by: Eli Lilly (Indianapolis, IN)
- Indication: Human use, Diabetes
- Date of approval: June 1996
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Translational Modifications:**
- **Structure:**
- **Additional Information:**

GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor)

- **Product name:** Leukine
- **Produced by:** Immunex (Seattle, WA)
- **Indication:** Human use, Bone marrow transplantation, Hodgkin's Disease, Leukemia
- **Date of approval:** Mar 91
- **Formulation:** Lyophilized solution which is reconstituted with sterile water (stored at refrigerated temperatures for < 6 hours) or 0.9% benzyl alcohol (can be stored for < 20 days at refrigerated

temperatures) and administered intravenous. After reconstitution, the lyophilized single use product contains either 0.25 mg/mL or 0.50 mg/mL GM-CSF, 40 mg/ml mannitol, 10 mg/ml sucrose, and 1.2 mg/ml tromethamine (final pH is 7.4 +/- 0.3). The reconstituted solution is then diluted into a 0.9% NaCl bag f r IV administration (note if final GM-CSF is below 0.01 mg/mL add human albumin to 0.1% to prevent adsorption to the IV bag.

- **Expression System:** Yeast (*S. Cerevisiae*)
- **Refolding Conditions:** None, expressed folded.
- **Structure:** Glycoprotein of 127 amino acids characterized by 3 primary molecular species having molecular masses of 19,500, 16800, and 15500 daltons. The primary sequence differs from natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from native.
- **Additional Information:** Specific activity is 5 X 10^7 colony forming units per mg protein. Sargramostim is the proper name for yeast-derived recombinant GM-CSF. Cost for a 0.5 mg GM-CSF vial is $178.

G-CSF (Granulocyte Colony Stimulating Factor)

- **Product name:** Neupogen
- **Produced by:** Amgen (Thousand Oaks, CA)
- **Indication:** Human use, Neutropenia, bone marrow transplantation, anemia
- **Date of approval:** Feb 91
- **Formulation:** Single-use solution formulation containing 0.3 mg/mL G-CSF, 10 mM sodium acetate, 5% mannitol, and 0.004% Tween-80 at a pH of 4. The product is to be stored at refrigerated temperatures and no more than 24 hours at room temperature. If required, Neupogen can be diluted with D5W (no not dilute with saline at any time; product may precipitate), at concentrations below 5 to 15μg/mL, add human albumin to 2 mg/mL to prevent adsorption to IV bag.
- **Expression System:** *E. coli.*
- **Refolding Conditions:**
- **Structure:** A 175 amino acid protein with a molecular weight of 18,800 daltons. The protein has an amino acid sequence identical to the human protein except for an additional N-terminal methionine (necessary for expression in *E. coli*). The human protein is glycosylated but the recombinant Neupogen is not.
- **Additional Information:** Sales > $500 million. Filgrastim is the name give to recombinant methionyl human G-CSF. Cost of therapy (lung cancer) is $2,130 (4.2 mg protein over 14 days). Specific activity is 30 million units per mg protein.

Satumomab Pendetide

- Product name: OncoScint CR/OV
- Produced by: Cytogen (Princeton, NJ)
- Indication: Human use, Colorectal and ovarian cancers
- Date of approval: Dec 92
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Translional Modifications:**
- **Structure:**
- **Additional Information:**

Interleukin-2

- **Product name:** Proleukin (generic name: Aldesieukin)
- **Produced by:** Chiron (Emeryville, CA)
- **Indication:** Human use, Renal cell carcinoma
- **Date of approval:** May 1992
- **Formulation:** Single-use lyophilized formulation which is reconstituted with 1.2 mL sterile water and administered intravenously. Each reconstituted product contains 1.1 mg/mL Proleukin, 50 mg/ml mannitol, and 0.18 mg/ml dibasic sodium phosphate (pH is 7.5 +/- 0.3). Lyophilized product is stored at refrigerated temperatures, reconstituted product is stable up to 48 hours at refrigerated to room temperatures, but should be stored in refrigerator due to lack of preservatives. Addition of preservatives results in increased aggregation, addition of human albumin alters pharmacology.
- **Expression System:** *E. coli* (tetracycline promoter).
- **Refolding Conditions:**

TABLE A

- **Structure:** Proleukin has a molecular weight of 15,300 daltons and differs from the natural human protein (is n t glycosylated, the N-terminal alanine is removed, and has a serine substituted for the free cysteine at position 125)
- **Additional Information:** Specific activity is 18 million international units per 1.1 mg protein. Cost is $395 per 1.3 mg protein.

Somatrem

- **Product name:** Protropin
- **Produced by:** Genentech (S. San Francisco, CA)
- **Indication:** Human use, Growth deficiency
- **Date of approval:** Oct 1985, patent expired on Oct 1992.
- **Formulation:** Lyophilized formulation which is reconstituted with 0.9% benzyl alcohol (supplied) and administered intramuscular or subcutaneous. The lyophilized vial contains 5 mg Somatrem, 40 mg mannitol and 1.7 mg sodium phosphates (0.1 mg sodium phosphate monobasic and 1.6 mg sodium phosphate dibasic) and is reconstituted with 1 to 5 mL of 0.9% benzyl alcohol. The lyophilized product is stored at refrigerated temperatures, the reconstituted product is good for 14 days at refrigerated temperatures.
- **Expression System:** *E. coli.*
- **Refolding Conditions:**
- **Structure:** Contains 192 amino acids with a molecular weight of 22,000 daltons. Identical to human sequence but contains an extra methionine at the N-terminus.
- **Additional Information:** Sales > $100 million. Cost of therapy is $13,110 (1 year, 313 mg protein)

DNase (deoxyribonuclease I)

- **Product name:** Pulmozyme
- **Produced by:** Genentech (S. San Francisco, CA)
- **Indication:** Human use, Cystic fibrosis
- **Date of approval:** Dec 1993
- **Formulation:** Inhalation solution (aerosol mist produced by a compressed air driven nebulizer system). Comes in a single-use 2.5 mL ampule containing 1.0 mg/mL DNase, 0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/ml sodium chloride, at a pH of 6.3. The solution is stored at refrigerated temperatures and should not be exposed to light.
- **Expression System:** Mammalian cells (Chinese hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 260 amino acids having a molecular weight of 37,000 daltons. The primary sequence is identical to that of the native human enzyme.
- **Additional Information:** Sales > $100 Million. Cost is $32 for 2.5 mg of protein (1 ampule)

M-CSF (Macrophage-Colony Stimulating Factor)

- **Product name:** Leucomax (generic name: Molgramostim)
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** FDA unapproved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Translational Modifications:**
- **Structure:**
- **Additional Information:**

Epoetin Beta (Erythropoietin)

- **Product name:** Marogen
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:**
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Translational Modifications:**

TABLE A

- **Structure:**
- **Additional Information:**

P lyribonucleotide
- **Product name:** Ampligen
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** FDA Unapproved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Human Serum Albumin
- **Product name:**
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:**
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Septomonab?
- **Product name:** Gentoxin
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** Not FDA approved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Protein
- **Product name:**
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:**
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

TABLE A

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Comvax™ *Haemophilus b* conjugate (meningococcal protein conjugate) and hepatitis b (recombinant) vaccine	Merck *Whitehouse Station, NJ.*	recombinant vaccine	vaccination of infants beginning at two months of age against both invasive *Haemophilus influenzae* type b diseases (Hib) and hepatitis B (October 1996)
Engerix-B® hepatitis B vaccine (recombinant)	SmithKline Beecham *Philadelphia, PA*	recombinant vaccine	hepatitis B (September 1989)
EPOGEN® Epoetin alfa (rEPO)	Amgen *Thousand Oaks, CA*	erythropoietin	treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir®-treated HIV-infected patients (June 1989); treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (April 1993); prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (December 1996)
PROCRIT® Epoetin alfa (rEPO)	Ortho Biotech *Raritan, NJ*	erythropoietin	treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir®-treated HIV-infected patients (December 1990); treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (April 1993); prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (December 1996)
[PROCRIT was approved for marketing under Amgen's epoetin alfa PLA. Amgen manufactures the product for Ortho Biotech.] Under an agreement between the two companies, Amgen licensed to Ortho Pharmaceutical the U.S. rights to epoetin alfa for indications for human use excluding dialysis and diagnostics.			
Genotropin™ somatropin (rDNA origin) for injection	Pharmacia & Upjohn *Kalamazoo, MI*	human growth hormone	short stature in children due to growth hormone deficiency (August 1995)
Geref® human growth hormone releasing factor	Serono Laboratories *Norwell, MA*	growth factor	evaluation of the ability of the somatotroph of the pituitary gland to secrete growth hormone (December 1990); pediatric growth hormone deficiency (October 1997)
Gonal-F® recombinant human follicle-stimulating hormone (r-FSH)	Serono Laboratories *Norwell, MA*	recombinant fertility hormone	female infertility (September 1997)
Humalog™ insulin lispro	Eli Lilly *Indianapolis, IN*	recombinant insulin	diabetes (June 1996)
Humatrope® somatropin (rDNA origin) for injection	Eli Lilly *Indianapolis, IN*	human growth hormone	human growth hormone deficiency in children (March 1987)

TABLE A

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Humulin® human insulin (recombinant DNA origin)	Eli Lilly *Indianapolis, IN*	recombinant insulin	diabetes (October 1982)
Infergen® interferon alfacon-1	Amgen *Thousand Oaks, CA*	interferon	treatment of chronic hepatitis C viral infection (October 1997)
Intron® A interferon alfa-2b (recombinant)	Schering-Plough *Madison, NJ*	interferon	hairy cell leukemia (June 1986); genital warts (June 1988); AIDS-related Kaposi's sarcoma (November 1988); hepatitis C (February 1991); hepatitis B (July 1992); malignant melanoma (December 1995); follicular lymphoma in conjunction with chemotherapy (November 1997)
KoGENate® antihemophiliac factor (recombinant)	Bayer Corporation, Pharmaceutical Division *West Haven, CT*	clotting factor	treatment of hemophilia A (February 1993)
Leukine™ sargramostim (GM-CSF)	Immunex *Seattle, WA*	colony stimulating factor	autologous bone marrow transplantation (March 1991); neutropenia resulting from chemotherapy in acute myelogenous leukemia (September 1995); allogeneic bone marrow transplantation (November 1995); peripheral blood progenitor cell mobilization and transplantation (December 1995)
MyoScint® imicromab pentetate	Centocor *Malvern, PA*	MAb	myocardial infarction imaging agent (July 1996)
Neumega® oprelvekin	Genetics Institute *Cambridge, MA*	MAb	prevention of severe chemotherapy-induced thrombocytopenia (November 1997)
NEUPOGEN® Filgrastim (rG-CSF)	Amgen *Thousand Oaks, CA*	colony stimulating factor	chemotherapy-induced neutropenia (February 1991); autologous or allogeneic bone marrow transplantation (June 1994); chronic severe neutropenia (December 1994); support peripheral blood progenitor cell transplantation (December 1995)
Norditropin® somatropin (rDNA origin) for injection	Novo Nordisk Pharmaceuticals *Princeton, NJ*	human growth hormone	treatment of growth failure in children due to inadequate growth hormone secretion (May 1995)
Novolin® 70/30 70% NPH human insulin isophane suspension & 30% regular, human insulin injection (recombinant DNA origin)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)
Novolin® L Lente®, human insulin zinc suspension (recombinant DNA origin)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)

TABLE A

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Novolin® N NPH, human insulin isophane suspension (recombinant DNA origin)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)
Novolin® R regular, human insulin injection (recombinant DNA origin)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)
Nutropin® somatropin for injection	Genentech *S. San Francisco, CA*	human growth hormone	growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (March 1994); Turner's syndrome (December 1996); growth hormone inadequacy in adults (December 1997)
Nutropin AQ™ somatropin (liquid)	Genentech *S. San Francisco, CA*	human growth hormone	growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (December 1995); Turner's syndrome (December 1996); growth hormone inadequacy in adults (December 1997)
OncoScint® CR/OV satumomab pendetide	CYTOGEN *Princeton, NJ*	MAb	detection, staging and follow-up of colorectal and ovarian cancers (December 1992)
ORTHOCLONE OKT®3 muromonab-CD3	Ortho Biotech *Raritan, NJ*	MAb	reversal of acute kidney transplant rejection (June 1986); reversal of heart and liver transplant rejection (June 1993)
Proleukin® aldesleukin (interleukin-2)	Chiron *Emeryville, CA*	interleukin	renal cell carcinoma (May 1992); metastatic melanoma (January 1998)
ProstaScint® capromab pentetate	CYTOGEN *Princeton, NJ*	MAb	detection, staging and follow-up of prostate adenocarcinoma (October 1996)
Protropin® somatrem for injection	Genentech *S. San Francisco, CA*	human growth hormone	human growth hormone deficiency in children (October 1985)
Pulmozyme® dornase alpha, recombinant	Genentech *S. San Francisco, CA*	recombinant DNase	cystic fibrosis (December 1993); management of advanced cystic fibrosis (December 1996)
Recombinate™ antihemophilic factor recombinant (rAHF)	Baxter Healthcare/ Hyland Division *Glendale, CA* Genetics Institute *Cambridge, MA*	clotting factor	hemophilia A (December 1992)
RECOMBIVAX HB® hepatitis B vaccine (recombinant), MSD	Merck *Whitehouse Station, NJ*	recombinant vaccine	hepatitis B prevention (July 1986)
Refludan™ lepirudin [rDNA] for injection	Hoechst Marion Roussel *Kansas City, MO*	recombinant anticoagulant	heparin-induced thrombocytopenia type II (March 1998)

TABLE A

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Regranex® becaplermin	Ortho-McNeil Pharmaceuticals *Raritan, NJ*	growth factor	lower extremity diabetic neuropathic ulcers (December 1997)
ReoPro® abciximab	Centocor *Malvern, PA* Eli Lilly *Indianapolis, IN*	MAb	anti-platelet prevention of blood clots in the setting of high-risk percutaneous transluminal coronary angioplasty (December 1994); refractory unstable angina when percutaneous coronary intervention is planned (November 1997)
Retavase™ reteplase	Boehringer Mannheim *Gaithersburg, MD* Centocor *Malvern, PA*	tissue plasminogen factor	treatment of acute myocardial infarction (October 1996)
Rituxan® rituximab	Genentech *S. San Francisco, CA* IDEC Pharmaceuticals *San Diego, CA*	MAb	treatment of relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma (November 1997);
Roferon®-A interferon alfa-2a, recombinant	Hoffmann-La Roche *Nutley, NJ*	interferon	hairy cell leukemia (June 1986); AIDS-related Kaposi's sarcoma (November 1988); chronic myelogenous leukemia (November 1995); hepatitis C (November 1996)
Saizen® somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	pediatric growth hormone deficiency (October 1996)
Serostim™ somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	treatment of AIDS-associated catabolism/wasting (August 1996); pediatric HIV failure to thrive (February 1998)
Verluma® nofetumomab	Boehringer Ingelheim *Ridgefield, CT* NeoRx *Seattle, WA*	MAb	detection of small-cell lung cancer (August 1996)
Vistide® cidofovir injection	Gilead Sciences *Foster City, CA*	nucleotide analogue	cytomegalovirus retinitis in AIDS patients (June 1996)
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ*	MAb	prevention of acute kidney transplant rejection (December 1997)

The content of this survey has been obtained through government and industry sources based on the latest information. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly.

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TABLE A

Biotechnology Medicines in Development

AIDS/HIV Infection and Related Conditions

Product Name	Company	Product Category	Indication	Development Status
AD-439 and AD-519 combination	Tanox Biosystems *Houston, TX*	MAb	HIV infection, AIDS	Phase II
AD-439 MAb, anti-HIV to V3 loop of gp120 protein; neutralizing antibody	Tanox Biosystems *Houston, TX*	MAb	HIV infection, AIDS	Phase II
AD-519 MAb, anti-HIV to C4 region of gp120 protein; neutralizing antibody	Tanox Biosystems *Houston, TX*	MAb	HIV infection, AIDS	Phase II
Alferon LDO® interferon alfa-n3	Interferon Sciences *New Brunswick, NJ*	interferon	AIDS-related complex, AIDS	Phase I/II
Alferon N Injection® interferon alfa-n3	Interferon Sciences *New Brunswick, NJ*	interferon	HIV infection (see also infectious diseases)	Phase III
			co-infection (HIV/HCV)	Phase II
ALVAC-MN 12-TMG (vCP205)	Pasteur Merieux Connaught *Lyons, France* Virogenetics *Albany, NY*	vaccine	HIV infection	Phase II
Ampligen®	Hemispherx Biopharma *New York, NY*	interferon	HIV infection (see also cancer, infectious diseases, other)	Phase II
autologous gene-modified hematopoietic stem cells	SyStemix *Palo Alto, CA*	gene therapy	HIV infection	Phase I
gene therapy	Cell Genesys *Foster City, CA* Hoechst Marion Roussel *Kansas City, MO*	gene therapy	HIV infection	Phase II
gp120 vaccine	VaxGen *S. San Francisco, CA*	vaccine	AIDS	Phase II
HIV-IT(V) Retrovector™ HIV-1 IIIB env/rev retroviral vector	Chiron Viagene *San Diego, CA*	gene therapy	asymptomatic HIV-1 infection	Phase II
HIV vaccine (gp120)	Chiron *Emeryville, CA*	vaccine	AIDS	Phase II
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	HIV disease (see also autoimmune, digestive, heart, neurologic, respiratory, skin)	Phase I

TABLE A

AIDS/HIV INFECTION AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
ISIS 2922 fomivirsen	Isis Pharmaceuticals *Carlsbad, CA*	antisense	cytomegalovirus retinitis	Phase III
ISIS 13312	Isis Pharmaceuticals *Carlsbad, CA*	antisense	cytomegalovirus retinitis	Phase I
Leukine™ sargramostim (GM-CSF)	Immunex *Seattle, WA*	colony stimulating factor	adjuvant to AIDS therapy, HIV infection, prevention of infection in HIVpatients (see also cancer)	Phase II
memantine	Neurobiological Technologies *Richmond, CA*		AIDS dementia complex and AIDS-related neuropathic pain (see also diabetes)	Phase II
MPL® immunomodulator vaccine	Ribi ImmunoChem *Hamilton, MT*	vaccine	AIDS (see also infectious diseases)	Phase I
NEUPOGEN® Filgrastim (rG-CSF)	Amgen *Thousand Oaks, CA*	colony stimulating factor	treatment and prevention of neutropenia in HIV patients (see also cancer, respiratory)	application submitted
Ovidrel® recombinant human chorionic gonadotropin (r-hCG)	Ares-Serono and Serono Laboratories *Norwell, MA*	recombinant gonadotropin	Kaposi's sarcoma, AIDS-related hypogonadism (see also infertility)	Phase I/II
PEG interleukin-2	Chiron *Emeryville, CA*	interleukin	HIV infection in combination with Retrovir®	Phase II
PMPA	Gilead Sciences *Foster City, CA*	nucleotide analogue	HIV infection, AIDS	Phase II
Preveon™ adefovir dipivoxil	Gilead Sciences *Foster City, CA*	nucleotide analogue	HIV infection, AIDS	Phase III
PRO 367	Progenics Pharmaceuticals *Tarrytown, NY*		HIV infection	Phase I
PRO 542	Progenics Pharmaceuticals *Tarrytown, NY*		HIV infection	Phase I
Proleukin® aldesleukin (interleukin-2)	Chiron *Emeryville, CA*	interleukin	HIV infection in combination with Retrovir® (see also cancer)	Phase II/III
Remune HIV-1 immunogen	Immune Response Corp. *Carlsbad, CA*	immune-based therapy	HIV seropositive	Phase III
retroviral vector with 2 ribozymes	Chiron *Emeryville, CA*	gene therapy	HIV infection	Phase I/II
TBC-3B (vaccinia virus expressing HIV genes env, gag and pol)	Therion Biologics *Cambridge, MA*	vaccine	AIDS prevention	Phase I

TABLE A

AUTOIMMUNE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
adenosine deaminase-transduced autologous CD34+ PBC or umbilical cord/ placental blood cells	National Cancer Institute *Bethesda, MD*	gene therapy	severe combined immunodeficiency	Phase I NCI TRIAL
adenosine deaminase-transduced T cells	National Cancer Institute *Bethesda, MD*	gene therapy	severe combined immunodeficiency	Phase I NCI TRIAL
AnergiX™-RA	Anergen *Redwood City, CA*	functional antigenics immuno-therapy	rheumatoid arthritis	Phase I
AnervaX™	Anergen *Redwood City, CA*	peptide vaccine	rheumatoid arthritis	Phase II
Avakine™ chimeric anti-TNF antibody	Centocor *Malvern, PA*	MAb	rheumatoid arthritis (see also digestive)	Phase III
CD40 ligand antibody	Biogen *Cambridge, MA*	MAb	lupus, immune thrombocytopenic purpura	Phase II
clenoliximab	IDEC Pharmaceuticals *San Diego, CA* SmithKline Beecham *Philadelphia, PA*	MAb	rheumatoid arthritis	Phase II
ConXn™ relaxin	Connetics *Palo Alto, CA*	recombinant human protein	scleroderma	Phase II
Enbrel tumor necrosis factor (TNF) receptor	Immunex *Seattle, WA* Wyeth-Ayerst Laboratories *Philadelphia, PA*	recombinant soluble receptor	rheumatoid arthritis	Phase III
h5G1.1	Alexion Pharmaceuticals *New Haven, CT*	MAb	lupus, rheumatoid arthritis	Phase I/II
IDEC-131 humanized MAb	IDEC Pharmaceuticals *San Diego, CA*	MAb	systemic lupus erythematosus	Phase I
IL-2 fusion protein $DAB_{389}IL\text{-}2$	Seragen *Hopkinton, MA*	fusion protein	severe rheumatoid arthritis (see also cancer, skin)	Phase I/II
Interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	rheumatoid arthritis (see also AIDS/HIV, digestive, heart, neurologic, respiratory, skin)	Phase II
IR 501 therapeutic vaccine	Immune Response Corp. *Carlsbad, CA*	vaccine	rheumatoid arthritis	Phase II
ISIS 2302	Isis Pharmaceuticals *Carlsbad, CA*	antisense	rheumatoid arthritis (see also digestive, skin, transplantation)	Phase II

TABLE A

AUTOIMMUNE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
MDX-33	Medarex *Annandale, NJ*	MAb	autoimmune diseases, idiopathic thrombocytopenic purpura	Phase I
ORTHOCLONE OKT4A	Ortho Biotech *Raritan, NJ*	MAb	treatment of CD4-mediated autoimmune diseases (see also transplantation)	Phase II
Quadraldine interleukin-4 (IL-4)	Schering-Plough *Madison, NJ*	interleukin	rheumatoid arthritis	Phase I
SMART™ Anti-CD3 HuM291	Protein Design Labs *Mountain View, CA*	MAb	autoimmune diseases (see also transplantation)	Phase I

BLOOD DISORDERS

Product Name	Company	Product Category	Indication	Development Status
CPC-111	Cypros Pharmaceuticals *Carlsbad, CA*	cellular therapy	sickle cell disease (see also heart)	Phase II
Factor VIII	Transkaryotic Therapies *Cambridge, MA*	gene therapy	hemophilia A	Phase I
CA-EPO	Hoechst Marion Roussel *Kansas City, MO* Transkaryotic Therapies *Cambridge, MA*	erythropoietin	anemia associated with chronic renal failure	Phase II
Kogenate-N rFVIII	Bayer *Berkeley, CA*	clotting factor	hemophilia A	Phase III
NovoSeven® recombinant factor VIIa	Novo Nordisk Pharmaceuticals *Princeton, NJ*	clotting factor	treatment of hemophilia A&Bwith and without antibodies against factors VIII/IX	Phase III
Optro™ recombinant human hemoglobin (rHb1.1)	Somatogen *Boulder, CO*	recombinant human hemoglobin	oxygen-carrying agent and alternative to red blood cell transfusion	Phase II
			stimulation of red blood cell formation	Phase I
ReFacto® recombinant factor VIII	Genetics Institute *Cambridge, MA*	clotting factor	hemophilia A	Phase III
YM-337 MAb	Yamanouchi USA *White Plains, NY* Protein Design Labs *Mountain View, CA*	MAb	platelet aggregation	Phase I

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
131I-chTNT-1/B	Techniclone *Tustin, CA*	MAb	malignant glioma	Phase I
Aastrom™ Cell Production System stem and progenitor cell expansion from bone marrow and umbilical cord blood	Aastrom Biosciences *Ann Arbor, MI*	cellular therapy	cancer immunosuppression/ blood and immune system recovery for patients receiving ablative chemotherapy	Phase II
Actimmune® interferon gamma-1b	National Cancer Institute *Bethesda, MD* Genentech *S. San Francisco, CA*	interferon	colon, lung, ovarian, prostate cancers, melanoma	Phase II NCI TRIAL
AFP-Scan™ technetium-99m-FAb' fragment (germ cell)	Immunomedics *Morris Plains, NJ*	MAb	extent of disease staging of liver and germ cell cancers	Phase II
allogeneic hematopoietic stem cell transplantation	SyStemix *Palo Alto, CA*	cellular therapy	advanced leukemia, lymphoma, myelodysplastic syndromes	Phase I
Allovectin-7 DNA/lipid complex encoding HLA-B7 antigen	Vical *San Diego, CA*	gene therapy	advanced metastatic melanoma, non-resectable squamous cell carcinoma of the head and neck	Phase II
ALT (autolymphocyte therapy)	Cellcor *Newton, MA* CYTOGEN *Princeton, NJ*	cellular therapy	metastatic renal cell carcinoma (kidney cancer)	Phase III completed
ALVAC-B7.1	National Cancer Institute *Bethesda, MD*	gene therapy	melanoma	Phase I NCI TRIAL
ALVAC-CEA-B7.1	National Cancer Institute *Bethesda, MD*	gene therapy	advanced adenocarcinomas	Phase I NCI TRIAL
ALVAC-CEA vaccine	National Cancer Institute *Bethesda, MD*	vaccine	advanced cancers	Phase I NCI TRIAL
ALVAC-IL-12 vaccine	National Cancer Institute *Bethesda, MD* Pasteur Merieux Connaught *Lyons, France*	vaccine	melanoma	Phase I NCI TRIAL
Ampligen®	Hemispherx Biopharma *New York, NY*	interferon	renal cancer (see also AIDS/HIV, infectious diseases, other)	Phase I/II
anti-cancer T-cell gene therapy	Cell Genesys *Foster City, CA*	gene therapy	colon cancer	Phase I/II
anti-idiotype monoclonal antibody	Novartis Pharmaceuticals *East Hanover, NJ*	MAb	cancer	Phase I

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
anti-Tac(Fv)-PE38 immunotoxin	National Cancer Institute *Bethesda, MD*	MAb+toxin	leukemia, lymphoma	Phase I NCI TRIAL
anti-transferrin receptor MAb	National Cancer Institute *Bethesda, MD*	MAb	advanced, refractory solid tumors	Phase I NCI TRIAL
anti-VEGF humanized MAb	Genentech *S. San Francisco, CA*	MAb	cancer	Phase I
autologous hematopoietic stem cells for autologous hematopoietic transplantation	SyStemix *Palo Alto, CA*	cellular therapy	hematopoietic reconstitution in patients with multiple myeloma, non-Hodgkin's lymphoma, breast cancer	Phase I/II
autologous peptide-specific activated lymphocytes	National Cancer Institute *Bethesda, MD*	cellular therapy	advanced solid tumors	Phase I NCI TRIAL
autologous transduced CD34+ bone marrow and peripheral blood stem cells	National Cancer Institute *Bethesda, MD*	gene therapy	breast cancer, myeloma	Phase I NCI TRIAL
Avicidin® MAb conjugate	Janssen Pharmaceutica *Titusville, NJ* NeoRx *Seattle, WA*	MAb	colorectal, lung, prostate cancers	Phase II
Avicine™ CTP-37	AVI BioPharma *Portland, OR*	vaccine	colorectal, pancreatic cancers	Phase II
Avonex® interferon beta-1A	Biogen *Cambridge, MA*	interferon	glioma (see also neurologic)	Phase II
B7 transfected allogeneic melanoma cell vaccine	National Cancer Institute *Bethesda, MD*	vaccine	melanoma	Phase I NCI TRIAL
BEC2, anti-idiotype MAb	ImClone Systems *Somerville, NJ*	vaccine	melanoma, small-cell lung cancer	Phase I
Betaseron® recombinant beta interferon-1b	National Cancer Institute *Bethesda, MD* Berlex Laboratories *Wayne, NJ*	interferon	non-small-cell lung cancer (see also neurologic)	Phase III NCI TRIAL
bispecific antibody	Chiron *Emeryville, CA*	MAb	cancer	Phase I
C225, anti-EGFR chimeric MAb	ImClone Systems *Somerville, NJ*	MAb	epidermal growth factor receptor positive cancers	Phase II
Campath 1H	LeukoSite *Cambridge, MA*	MAb	chronic lymphocytic leukemia	In clinical trials

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
carcinoembryonic antigen peptide-1 vaccine	National Cancer Institute *Bethesda, MD*	vaccine	breast, gastrointestinal tract, lung cancers	Phase I NCI TRIAL
CEACide™ humanized anti-CEA antibody (hMN14)	Immunomedics *Morris Plains, NJ*	MAb	colorectal cancer	Phase II
CEA-Scan™ technetium-99m-arcitumomab (breast)	Immunomedics *Morris Plains, NJ*	MAb	extent of disease staging of breast cancer	Phase II
CEA-Scan™ technetium-99m-arcitumomab (lung)	Immunomedics *Morris Plains, NJ*	MAb	extent of disease staging of lung cancer	Phase III
CEAVac™ anti-idiotype antibody vaccine	Titan Pharmaceuticals *S. San Francisco, CA*	vaccine	colorectal cancer	Phase II
cell therapy	CytoTherapeutics *Providence, RI*	cellular therapy	cancer pain, untreatable/unrelieved by other forms of treatment	Phase II
Cereport™ (RMP-7) and carboplatin	Alkermes *Cambridge, MA*		recurrent malignant brain tumor	Phase III
chemotherapy-resistant bone marrow	Genetix *Rye, NY*	gene therapy	treatment of cancer patients requiring chemotherapy	Phase I/II
chimeric MAb 14.18	National Cancer Institute *Bethesda, MD*	MAb	melanoma, neuroblastoma	Phase II NCI TRIAL
CM 101	CarboMed *Brentwood, TN*		cancer	Phase I/II
CMA-676	Wyeth-Ayerst Laboratories *Philadelphia, PA*	MAb	relapsed acute myelogenous leukemia	Phase II/III
CMB-401	Wyeth-Ayerst Laboratories *Philadelphia, PA*	MAb	ovarian cancer	Phase I/II
colon cancer cell line vaccine	Immune Response Corp. *Carlsbad, CA* Sidney Kimmel Cancer Center *San Diego, CA*	vaccine	colon cancer	Phase I
CP-358,774	OSI Pharmaceuticals *Uniondale, NY* Pfizer *New York, NY*	cellular therapy	cancer	Phase I
CT-2584	Cell Therapeutics *Seattle, WA*		ovarian, prostate cancer, sarcoma	Phase I
cytosine deaminase gene-adenoviral vector	GenVec *Rockville, MD*	gene therapy	colon cancer	Phase I

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
DA/Hu(gamma).4 [hIFN-γ(V)] Retrovector™ hIFN-γ retroviral vector	Chiron Viagene *San Diego, CA*	gene therapy	metastatic melanoma	Phase I
DA/Hu(gamma).15-transduced autologous tumor cells and interferon-gamma expressing transduced autologous tumor cells (combination therapy)	Chiron Viagene *San Diego, CA*	gene therapy	stage IV malignant melanoma	Phase I
DA/Hu(gamma).15-transduced autologous tumor cells; ITAT	Chiron Viagene *San Diego, CA*	gene therapy	disseminated malignant melanoma	Phase I
daniplestim	Searle *Skokie, IL*	growth factor	mobilization of peripheral blood stem cells	Phase III
dendritic cell therapy	Dendreon *Mountain View, CA*	cellular therapy	advanced prostate cancer	Phase II/III
			multiple myeloma	Phase I
E/A lipid complex (tgDCC-E/A)	Targeted Genetics *Seattle, WA*	gene therapy	breast, head and neck, ovarian cancers	Phase I
EGF fusion protein $DAB_{389}EGF$	Seragen *Hopkinton, MA*	fusion protein	non-small-cell lung cancer	Phase I/II
EPREX® erythropoietin	National Cancer Institute *Bethesda, MD* Ortho Biotech *Raritan, NJ*	erythropoietin	neuroblastoma	Phase II NCI TRIAL
ERB-38 immunotoxin fusion protein (recombinant)	National Cancer Institute *Bethesda, MD*	fusion protein	advanced stage solid tumors	Phase I NCI TRIAL
Ewing's sarcoma and alveolar rhabdomyosarcoma peptide vaccine	National Cancer Institute *Bethesda, MD*	vaccine	sarcoma	Phase I NCI TRIAL
FLT3 ligand	National Cancer Institute *Bethesda, MD* Immunex *Seattle, WA*	growth factor	melanoma, renal cell cancer	Phase I NCI TRIAL
G3139	Genta *San Diego, CA*	antisense	cancer	Phase I
gamma interferon gene therapy	Chiron *Emeryville, CA*	gene therapy	cancer	Phase I

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Gastrimmune™ neutralizing G17 hormone	Aphton *Woodland, CA*	vaccine	colorectal, pancreatic, stomach cancers (see also digestive)	Phase I/II
GeneVax® gene vaccine	Centocor *Malvern, PA*	vaccine	colorectal cancer	Phase I
GLI-328	Genetic Therapy *Gaithersburg, MD*	gene therapy	glioblastoma multiforme	Phase III
GM-CSF cellular cancer vaccine	Powderject Vaccines *Madison, WI*	vaccine	melanoma, sarcoma	Phase I
GMK ganglioside antigen	Bristol-Myers Squibb *Princeton, NJ* Progenics Pharmaceuticals *Tarrytown, NY*	vaccine	prevent recurrence following surgery to remove primary melanoma	Phase III
gp100 adenovirus vaccine	National Cancer Institute *Bethesda, MD* Genzyme Molecular Oncology *Cambridge, MA*	vaccine	melanoma	Phase I NCI TRIAL
gp100 peptide vaccine	National Cancer Institute *Bethesda, MD*	vaccine	melanoma	Phase I NCI TRIAL
GVAX™ cancer vaccine	Cell Genesys *Foster City, CA*	vaccine	prostate, lung cancers, melanoma	Phase I/II
HER-2/neu peptide vaccine	National Cancer Institute *Bethesda, MD*	vaccine	breast, colorectal, ovarian, prostate cancers	Phase I NCI TRIAL
Herceptin™ trastuzumab (anti-HER-2 humanized MAb)	Genentech *S. San Francisco, CA*	MAb	breast cancer	Phase III completed
HPV 16, E6 and E7 peptide vaccine	National Cancer Institute *Bethesda, MD*	vaccine	cervical cancer	Phase I NCI TRIAL
HPV E7 lipopeptide vaccine	National Cancer Institute *Bethesda, MD* Cytel *San Diego, CA*	vaccine	cervical cancer	Phase I NCI TRIAL
HPV vaccine	MedImmune *Gaithersburg, MD* SmithKline Beecham *Philadelphia, PA*	vaccine	cervical cancer (see also infectious diseases)	Phase I
HSPPC-96 (autologous tumor derived)	Antigenics *New York, NY*	heat shock protein	melanoma, pancreatic, renal cell cancers	Phase I
human growth hormone	Transkaryotic Therapies *Cambridge, MA*	gene therapy	cancer cachexia (muscle wasting)	Phase I
IDEC-InB8	IDEC Pharmaceuticals *San Diego, CA*	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II
IDEC-Y2B8	IDEC Pharmaceuticals *San Diego, CA*	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Leucotropin GM-CSF	Cangene *Mississauga, Ontario*	colony stimulating factor	mobilization of peripheral blood stem cells in patients with adjuvant breast cancer	Phase III
Leukine™ sargramostim (GM-CSF)	Immunex *Seattle, WA*	colony stimulating factor	prophylaxis and treatment of chemotherapy-induced neutropenia, prophylaxis of chemotherapy-induced neutropenia in acute myelogenous leukemia (see also AIDS/HIV)	application submitted
Leuvectin DNA/lipid complex encoding IL-2	Vical *San Diego, CA*	gene therapy	prostate cancer, renal cell carcinoma, melanoma, sarcoma	Phase I
LP 2307	LIDAK Pharmaceuticals *La Jolla, CA*	vaccine	malignant melanoma	Phase I/II
LR-3001	Inex Pharmaceuticals *Hayward, CA*	antisense	chronic myelogenous leukemia in accelerated phase or blast crisis	Phase I
LYM-1	Techniclone *Tustin, CA*	MAb	lymphoma	Phase II/III
Lymphocide™ anti-CD22 humanized MAb	Immunomedics *Morris Plains, NJ*	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II
LymphoScan™ technetium-99m-bectumomab (lymphoma)	Immunomedics *Morris Plains, NJ*	MAb	extent of disease staging of non-Hodgkin's B-cell lymphoma, detection of residual disease following radiation/chemotherapy	Phase III
MAb	Glaxo Wellcome *Rsch. Triangle Park, NC*	MAb	lung, prostate cancers	Phase II
MART-1 adenovirus vaccine	National Cancer Institute *Bethesda, MD* Genzyme Molecular Oncology *Cambridge, MA*	vaccine	melanoma	Phase I NCI TRIAL
MART-1 melanoma vaccine	National Cancer Institute *Bethesda, MD*	vaccine	metastatic melanoma	Phase I NCI TRIAL
MDRx1™	Titan Pharmaceuticals *S. San Francisco, CA*	gene therapy	enable high-dose chemotherapy with reduced side effects	Phase I
MDX-447 bispecific antibody	Medarex *Annandale, NJ*	MAb	head and neck, renal cancers	Phase I/II
MDX-H210 bispecific antibody	Medarex *Annandale, NJ*	MAb	breast, colorectal, kidney, ovarian, prostate cancers	Phase I/II
Melacine® melanoma theraccine (therapeutic vaccine)	Ribi ImmunoChem *Hamilton, MT*	vaccine	stage IV melanoma with interferon alpha	Phase III completed
	Ribi ImmunoChem *Hamilton, MT* Southwest Oncology Group *San Antonio, TX*	vaccine	stage II melanoma in patients with no evidence of disease to prevent recurrence following surgery to remove primary disease	Phase III

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
myeloid progenitor inhibitory factor-1	Human Genome Sciences *Rockville, MD*	interleukin	chemoprotection	Phase I
myeloma-derived idiotypic antigen vaccine	National Cancer Institute *Bethesda, MD*	vaccine	multiple myeloma	Phase I NCI TRIAL
NEUPOGEN® Filgrastim (rG-CSF)	Amgen *Thousand Oaks, CA*	colony stimulating factor	acute myelogenous leukemia (see also AIDS/HIV, respiratory)	application submitted
Oncaspar® PEG-L-asparaginase	Enzon *Piscataway, NJ* Rhone-Poulenc Rorer *Titusville, NJ*		first-line treatment of acute lymphoblastic leukemia (ALL) adult ALL, non-Hodgkin's lymphoma, chronic lymphocytic leukemia	in clinical trials
Oncolym®	Techniclone *Tustin, CA*	MAb	malignant glioma	Phase I
OncoRad® PR CYT-356-Y-90	CYTOGEN *Princeton, NJ*	MAb	targeted radiotherapy for prostate malignancies	Phase II
OncoScint® CR/OV satumomab pendetide	CYTOGEN *Princeton, NJ*	MAb	detection, staging and follow-up of breast cancer	Phase II
ONYX-015	Onyx Pharmaceuticals *Richmond, CA*	oncolytic virus therapy	p53 deficient cancers	Phase I/II
p53 and RAS vaccine	National Cancer Institute *Bethesda, MD*	vaccine	solid tumors	Phase I NCI TRIAL
p53 tumor suppressor gene	Schering-Plough *Madison, NJ*	gene therapy	lung cancer	Phase II
			solid tumors that carry the p53 gene mutation or deletion	Phase I
Panorex® edrecolomab	Centocor *Malvern, PA*	MAb	adjuvant therapy for post-operative colorectal cancer	Phase III
peripheral blood lymphocytes transduced with a gene encoding a chimeric T-cell receptor	National Cancer Institute *Bethesda, MD*	gene therapy	ovarian cancer	Phase I NCI TRIAL
Proleukin® aldesleukin (interleukin-2)	Chiron *Emeryville, CA*	interleukin	acute myelogenous leukemia, non-Hodgkin's lymphoma (see also AIDS/HIV)	Phase II/III
promegapoietin	Searle *Skokie, IL*	growth factor	adjunctive hematopoietic therapy following chemotherapy	Phase I
Prostvac recombinant vaccinia virus	Therion Biologics *Cambridge, MA*	vaccine	prostate cancer	Phase I/II

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
RAS 5-17 peptide vaccine	National Cancer Institute *Bethesda, MD*	vaccine	solid tumors	Phase I NCI TRIAL
rCEA Vaccine recombinant carcinoembryonic antigen	Protein Sciences *Meriden, CT*	vaccine	breast, colon cancers	Phase I
Rebif® recombinant interferon beta-1a	Serono Laboratories *Norwell, MA*	interferon	colorectal cancer (see also infectious diseases, neurologic)	Phase III
			non-small-cell lung cancer	Phase I/II
recombinant human interleukin-12 (rhIL-12)	Genetics Institute *Cambridge, MA* Wyeth-Ayerst Laboratories *Philadelphia, PA*	interleukin	cancer (see also infectious diseases)	Phase I/II
retroviral vector with tumor necrosis factor gene	Chiron *Emeryville, CA*	gene therapy	melanoma	Phase I
rF-gp100 (recombinant fowlpox virus)	Therion Biologics *Cambridge, MA*	vaccine	melanoma	Phase I
rF-MART-1 (recombinant fowlpox virus)	Therion Biologics *Cambridge, MA*	vaccine	melanoma	Phase I
RIGScan® CR49 125 I-cc49 MAb	Neoprobe *Dublin, OH*	MAb	colorectal cancer	application submitted
Rituxan® rituximab	National Cancer Institute *Bethesda, MD* IDEC Pharmaceuticals *San Diego, CA*	MAb	leukemia, lymphoma	Phase II NCI TRIAL
Roferon®-A interferon alfa-2a, recombinant	Hoffmann-La Roche *Nutley, NJ*	interferon	malignant melanoma adjuvant	Phase III
rV-gp100 (recombinant vaccinia virus)	Therion Biologics *Cambridge, MA*	vaccine	melanoma	Phase I
rV-MART-1 (recombinant vaccinia virus)	Therion Biologics *Cambridge, MA*	vaccine	melanoma	Phase I
Serostim™ somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	cancer cachexia (see also other)	Phase I/II
Sigosix® recombinant interleukin-6 (r-IL-6)	Ares-Serono and Serono Laboratories *Norwell, MA*	interleukin	hematological conditions (myelodysplastic syndromes, cancer)	Phase I/II

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
SMART™ M195 HuM195	Protein Design Labs *Mountain View, CA*	MAb	acute myeloid leukemia	Phase II/III
			acute promyelocytic leukemia	Phase II
			advanced myeloid leukemia (with Bismuth-213)	Phase I
stem cell factor	Amgen *Thousand Oaks, CA*	stem cell factor	adjunct to chemotherapy	application submitted
SU101	SUGEN *Redwood City, CA*	PDGF-receptor tyrosine kinase inhibitor	malignant glioma	Phase III
			prostate cancer	Phase II
			solid tumors	Phase I/II
SU5416	SUGEN *Redwood City, CA*	angiogenesis inhibitor	solid tumors	Phase I
TBC CEA (vaccinia virus expressing carcinoembryonic antigen)	Therion Biologics *Cambridge, MA*	vaccine	colorectal and lung cancers	Phase I/II
TCell-HDM	Coulter Cellular Therapies *Boston, MA*	cellular therapy	cancer	Phase I/II
Theratope® synthetic carbohydrate therapeutic vaccine	Biomira *Edmonton, Alberta* Chiron *Emeryville, CA*	vaccine	breast cancer	Phase II completed
thrombopoietin	Genentech *S. San Francisco, CA*	erythropoietin	thrombocytopenia related to cancer treatment	Phase II
Thyrogen® recombinant human thyroid-stimulating hormone	Genzyme *Cambridge, MA*		detection and treatment of thyroid cancer metastases	application submitted
TNT	Techniclone *Tustin, CA*	MAb	non-Hodgkin's B-cell lymphoma	Phase II/III
			solid tumors	Phase I
TriAB™ anti-idiotype antibody vaccine	Titan Pharmaceuticals *S. San Francisco, CA*	vaccine	breast cancer	Phase II
TriGEM™ anti-idiotype antibody vaccine	Titan Pharmaceuticals *S. San Francisco, CA*	vaccine	small-cell lung cancer, melanoma	Phase I
urate oxidase (recombinantly-produced enzyme)	Sanofi *New York, NY*	recombinant enzyme	prophylaxis for chemotherapy-related hyperuricemia, treatment of cancer-related hyperuricemia	Phase III

TABLE A

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
vaccinia-CEA 180KD vaccine	National Cancer Institute *Bethesda, MD* Therion Biologics *Cambridge, MA*	vaccine	advanced colorectal cancer	Phase I NCI TRIAL
Vaxid anti-idiotype DNA vaccine	Vical *San Diego, CA*	vaccine	B-cell and mantle cell lymphomas	Phase I
Xerecept™ human corticotropin-releasing factor (hCRF)	Neurobiological Technologies *Richmond, CA*		brain tumor edema	Phase II
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	certain blood cancers (see also eye, neurologic, skin, transplantation)	Phase II

DIABETES AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Beta Kine transforming growth factor-beta 2	Genzyme Tissue Repair *Cambridge, MA*	growth factor	chronic diabetic foot ulcers	Phase II
BetaRx-H encapsulated human islets	VivoRx *Santa Monica, CA*	cellular therapy	insulin-dependent diabetes	Phase I
BetaRx-P encapsulated porcine islets	VivoRx *Santa Monica, CA*	cellular therapy	insulin-dependent diabetes	Phase I
BetaRx-Pr encapsulated proliferated human islets	VivoRx *Santa Monica, CA*	cellular therapy	insulin-dependent diabetes	Phase I
Glucagen™ recombinant human glucagon (protein)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant human protein	hypoglycemia (see also digestive)	Phase III
glucagon for injection (rDNA origin)	Eli Lilly *Indianapolis, IN*	recombinant human protein	to treat severe hypoglycemic events in patients with diabetes and to aid in gastrointestinal diagnostic procedures	application submitted
insulinotropin	Scios *Mountain View, CA*		type 2 diabetes	Phase II
memantine	Neurobiological Technologies *Richmond, CA*		painful diabetic neuropathy (see also AIDS/HIV)	Phase II
nerve growth factor	Genentech *S. San Francisco, CA*	growth factor	diabetic peripheral neuropathy	Phase III

TABLE A

DIABETES AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
pimagedine	Alteon *Ramsey, NJ* Genentech *S. San Francisco, CA*		diabetic progressive kidney disease, diabetic end-stage kidney disease (see also neurologic)	Phase III
pramlintide	Amylin Pharmaceuticals *San Diego, CA*	human amylin analog	improved metabolic control, which includes glucose, weight and lipid profiles in type 1 and insulin-using type 2 diabetes	Phase III
rDNA insulin	Inhale Therapeutic Systems *Palo Alto, CA*	recombinant insulin	diabetes	Phase II
Trovert™	Sensus *Austin, TX*	human growth hormone	diabetes-related illnesses (see also growth disorders)	Phase II

DIGESTIVE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Avakine™ chimeric anti-TNF antibody	Centocor *Malvern, PA*	MAb	Crohn's disease (see also autoimmune)	application submitted
Gastrimmune™ neutralizing G17 hormone	Aphton *Woodland, CA*	vaccine	gastroesophageal reflux disease, peptic and nonsteroidal anti-inflammatory drug ulcers (see also cancer)	Phase I/II
Glucagen™ recombinant human glucagon (protein)	Novo Nordisk Pharmaceuticals *Princeton, NJ*	recombinant human protein	gastrointestinal motility inhibition (see also diabetes)	Phase III
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	Crohn's disease, ulcerative colitis (see also AIDS/HIV, autoimmune, heart, neurologic, respiratory, skin)	Phase II
ISIS 2302	Isis Pharmaceuticals *Carlsbad, CA*	antisense	Crohn's disease, ulcerative colitis (see also autoimmune, skin, transplantation)	Phase II
LDP-02	Genentech *S. San Francisco, CA* LeukoSite *Cambridge, MA*	MAb	inflammatory bowel disease	Phase II
LeukoScan® sulesomab	Immunomedics *Morris Plains, NJ*	MAb	inflammatory bowel disease (see also infectious diseases)	Phase II
Neumega® recombinant human interleukin-11	Genetics Institute *Cambridge, MA*	interleukin	Crohn's disease	Phase II
recombinant platelet activating factor-acetylhydrolase (rPAF-AH)	ICOS *Bothell, WA*		pancreatitis (see also respiratory)	Phase II

TABLE A

EYE CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
BPD-MA verteporfin	QLT PhotoTherapeutics *Vancouver, British Columbia*		age-related macular degeneration	Phase III
MDX-RA immunotoxin	Medarex *Annandale, NJ*	MAb	prevention of secondary cataract	Phase III
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	uveitis (see also cancer, neurologic, skin, transplantation)	Phase I/II

GENETIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
AAV CFTR gene therapy	Targeted Genetics *Seattle, WA*	gene therapy	cystic fibrosis (see also respiratory)	Phase I
CFTR/adenovirus vector	Genzyme *Cambridge, MA*	gene therapy	cystic fibrosis	Phase I
CFTR/lipid vector	Genzyme *Cambridge, MA*	gene therapy	cystic fibrosis	Phase I
ex vivo stem cells/ retrovirus vector	Genzyme *Cambridge, MA*	gene therapy	Gaucher's disease	Phase I
GR213487B	Glaxo Wellcome *Rsch. Triangle Park, NC* Megabios *Burlingame, CA*	gene therapy	cystic fibrosis	Phase I/II
GV-10	GenVec *Rockville, MD*	gene therapy	cystic fibrosis	Phase I
HP-3	Milkhaus Laboratory *Boxford, MA*	signalling	cystic fibrosis	Phase II
Neuprex™ recombinant human bactericidal/ permeability-increasing protein (rBPI-21)	XOMA *Berkeley, CA*	recombinant human protein	cystic fibrosis exacerbations (see also infectious diseases, other)	Phase I
Pulmozyme® domase alpha, recombinant	Genentech *S. San Francisco, CA*	recombinant DNase	early intervention in cystic fibrosis	Phase III
x-galactosidase A	Transkaryotic Therapies *Cambridge, MA*	enzyme	Fabry's disease	Phase I

TABLE A

GROWTH DISORDERS

Product Name	Company	Product Category	Indication	Development Status
pralmorelin (GPA-748)	Wyeth-Ayerst Laboratories *Philadelphia, PA*	human growth hormone	adult growth hormone deficiency	Phase I
ProLease® hGH	Alkermes *Cambridge, MA* Genentech *S. San Francisco, CA*	human growth hormone	growth hormone deficiency in children	Phase III
Saizen® somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	management of adults with growth hormone disorder, intrauterine growth retardation in children (see also other)	Phase III
Trovert™	Sensus *Austin, TX*	human growth hormone	acromegaly (see also diabetes)	Phase II

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
AcuTect™ Tc-99m apcitide	Diatide *Londonderry, NH*	peptide	detection of carotid thrombus	Phase II
anti-CD18 humanized MAb	Genentech *S. San Francisco, CA*	MAb	acute myocardial infarction	Phase II
BioByPass™ therapeutic angiogenesis (VEGF)	CenVec *Rockville, MD*	gene therapy	cardiovascular disease, including cardiac artery disease and peripheral vascular disease, either as an adjunct or alternative to existing surgical approaches such as cardiac artery bypass grafts and angioplasty	Phase I
Biostent™	NeoRx *Seattle, WA*		reduction of restinosis (vascular remodeling) following balloon angioplasty	Phase I
Capiscint	Centocor *Malvern, PA*	MAb	atherosclerotic plaque imaging agent	Phase I
Corsevin™ M 12D10-Fab	Centocor *Malvern, PA* Corvas *San Diego, CA*	MAb	thrombolytic complications of percutaneous transluminal coronary angioplasty, coronary arterial starts, disseminates intravascular coagulation	Phase I
CPC-111	Cypros Pharmaceuticals *Carlsbad, CA*	cellular therapy	coronary bypass surgery (see also blood)	Phase II
factor VIIa inhibitors	Corvas *San Diego, CA*		deep vein thrombosis, pulmonary embolism, unstable angina, myocardial infarction	Phase I
FIBLAST® trafermin	Scios *Mountain View, CA* Wyeth-Ayerst Laboratories *Philadelphia, PA*	growth factor	peripheral vascular disease, coronary artery disease (see also neurologic)	Phase II

TABLE A

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
gene therapy	Collateral Therapeutics *San Diego, CA*	gene therapy	stable exertional angina	Phase I/II
growth factor	Chiron *Emeryville, CA*	growth factor	coronary artery disease	Phase I
h5G1.1-SCFV (recombinant)	Alexion Pharmaceuticals *New Haven, CT* Enzon *Piscataway, NJ*		cardiopulmonary bypass-associated inflammation using SCD® technology	Phase II
Hu23F2G MAb	ICOS *Bothell, WA*	MAb	myocardial infarction (see also neurologic, other)	Phase II
Integrilin™ eptifibatide (IIb/IIIa platelet aggregation inhibitor)	COR Therapeutics *S. San Francisco, CA* Schering-Plough *Madison, NJ*		percutaneous transluminal coronary angioplasty, unstable angina	application submitted
			acute myocardial infarction	Phase II
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	ischemic reperfusion injury (see also AIDS/HIV, autoimmune, digestive, neurologic, respiratory, skin)	Phase I
lanoteplase	Bristol-Myers Squibb *Princeton, NJ*	t-PA	acute myocardial infarction	Phase III
LR-3280	Inex Pharmaceuticals *Vancouver, BC* Schwarz Pharma *Milwaukee, WI*	antisense	cardiovascular restinosis	Phase II
MH1-Fab' imaging agent	American Biogenetic Sciences *Boston, MA*	MAb	in vivo imaging agent for the detection of cardiovascular thrombosis	Phase I/II
MPL®-C immunomodulator	Ribi ImmunoChem *Hamilton, MT*		prevention/amelioration of cardiac ischemia reperfusion injury	Phase II
Natrecor® BNP	Scios *Mountain View, CA*		acute congestive heart failure	Phase III completed/ application submitted
			cardiovascular pulmonary surgery	Phase I
Novastan® argatroban	Texas Biotechnology *Houston, TX*		heparin-induced thrombocytopenia thrombosis syndrome	application submitted
ReoPro® abciximab	Centocor *Malvern, PA* Eli Lilly *Indianapolis, IN*	MAb	unstable angina (see also neurologic)	Phase III
			acute myocardial infarction	Phase II
rhAntithrombin III (recombinant)	Genzyme *Cambridge, MA*		control of blood clotting during coronary artery bypass surgery	Phase II completed
TNK (second-generation t-PA)	Genentech *S. San Francisco, CA*	t-PA	acute myocardial infarction	Phase III

TABLE A

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
TP10	T Cell Sciences *Needham, MA*	recombinant soluble receptor	heart attack (see also respiratory, transplantation)	Phase I
VEGF	Genentech *S. San Francisco, CA*	growth factor	coronary artery disease	Phase I
VEGF 121 (vascular endothelial growth factor)	Scios *Mountain View, CA*	growth factor	cardiovascular disorders	Phase I
Xubix™ sibratiban oral IIb/IIIa antagonist	Genentech *S. San Francisco, CA*		acute coronary syndrome	Phase III

INFECTIOUS DISEASES

Product Name	Company	Product Category	Indication	Development Status
adefovir dipivoxil	Gilead Sciences *Foster City, CA*	nucleotide analogue	hepatitis B	Phase II
Alferon N Gel® interferon alfa-n3	Interferon Sciences *New Brunswick, NJ*	interferon	human papillomavirus infections	Phase II
Alferon N Injection® interferon alfa-n3	Interferon Sciences *New Brunswick, NJ*	interferon	chronic hepatitis C infections (see also AIDS/HIV)	Phase III
			genital warts	Phase II
Ampligen®	Hemispherx Biopharma *New York, NY*	interferon	hepatitis (see also AIDS/HIV, cancer, other)	Phase I/II
anti-tumor necrosis factor MAb	Chiron *Emeryville, CA*	MAb	sepsis	Phase II/III
Campylobacter vaccine	Antex Biologics *Gaithersburg, MD*	cellular vaccine	traveler's diarrhea (*Campylobacter* infections)	Phase II
CMV vaccine	Chiron *Emeryville, CA*	vaccine	cytomegalovirus infection	Phase II
DTaP vaccine	Chiron *Emeryville, CA*	vaccine	diphtheria, tetanus, acellular pertussis	Phase III
Epstein-Barr virus vaccine	Aviron *Mountain View, CA* SmithKline Beecham *Philadelphia, PA*	recombinant subunit vaccine	prevention of Epstein-Barr virus infection (cause of mononucleosis infection)	Phase I
genital herpes vaccine	Glaxo Wellcome *Rsch. Triangle Park, NC*	vaccine	genital herpes	Phase I
Helicobacter vaccine	Antex Biologics *Gaithersburg, MD*	cellular vaccine	peptic ulcers (*Helicobacter pylori* infections)	Phase I

TABLE A

INFECTIOUS DISEASES

Product Name	Company	Product Category	Indication	Development Status
hepatitis A vaccine	Chiron *Emeryville, CA*	vaccine	hepatitis A	Phase III
hepatitis B DNA vaccine	PowderJect Vaccines *Madison, WI*	DNA vaccine	hepatitis B prevention	Phase I
hepatitis B vaccine (recombinant)	SmithKline Beecham *Philadelphia, PA*	vaccine	treatment of hepatitis B	Phase II
herpes simplex vaccine (recombinant)	SmithKline Beecham *Philadelphia, PA*	vaccine	prevention of herpes simplex infection	Phase III
HPV vaccine	MedImmune *Gaithersburg, MD* SmithKline Beecham *Philadelphia, PA*	vaccine	genital warts (see also cancer)	Phase I
human anti-hepatitis B antibody (OST 577)	Protein Design Labs *Mountain View, CA*	MAb	liver transplantation due to chronic hepatitis B infection	Phase I/II completed
Intron® A interferon alfa-2b (recombinant)	Schering-Plough *Madison, NJ*	interferon	pediatric hepatitis B, self-injectable dosing system for hepatitis C (see also cancer)	application submitted
			hepatitis C (PEG-Intron A)	Phase III
Intron® A/ Rebetol™ interferon alfa-2b (recombinant)/ ribavirin	Schering-Plough *Madison, NJ*	interferon	relapsed hepatitis C	application submitted
			naive hepatitis C (not previously treated with interferon)	Phase III
			hepatitis C (PEG-Intron A/Rebetol)	Phase I
LeukoScan® sulesomab	Immunomedics *Morris Plains, NJ*	MAb	diagnosis of osteomyelitis, infected prosthesis, appendicitis (see also digestive)	application submitted
Lyme borreliosis protein vaccine	Pasteur Merieux Connaught *Swiftwater, PA*	vaccine	Lyme disease	Phase III
Lyme disease vaccine (recombinant)	SmithKline Beecham *Philadelphia, PA*	vaccine	prevention of Lyme disease	application submitted
MAK 195F	Knoll Pharmaceutical *Mt. Olive, NJ*	MAb	sepsis	Phase III
MEDI-491 parvovirus B 19 vaccine	MedImmune *Gaithersburg, MD*	vaccine	B 19 parvovirus-induced miscarriages and anemia	Phase I
meningococcus C vaccine	Chiron *Emeryville, CA*	vaccine	meningococcus C	Phase II

TABLE A

INFECTIOUS DISEASES

Product Name	Company	Product Category	Indication	Development Status
MPL® immunomodulator (25+ antigens for adult and pediatric applications)	Ribi ImmunoChem *Hamilton, MT*	vaccine	infectious diseases (see also AIDS/HIV)	in clinical trials
Neuprex™ recombinant human bactericidal/ permeability-increasing protein (rBPI-21)	XOMA *Berkeley, CA*	recombinant human protein	meningococcemia (see also genetic, other)	Phase III
			antibiotic adjuvant in intra-abdominal infections	Phase II
Protovir™ human anti-CMV antibody	Protein Design Labs *Mountain View, CA*	MAb	cytomegalovirus infections in bone marrow transplant patients	Phase II completed
Rebif® recombinant interferon beta-1a	Serono Laboratories *Norwell, MA*	interferon	viral infections (see also cancer, neurologic)	Phase II/III
recombinant human activated protein C (rhAPC)	Eli Lilly *Indianapolis, IN*	recombinant human protein	treatment of severe sepsis	Phase II
recombinant human interleukin-12 (rhIL-12)	Genetics Institute *Cambridge, MA* Wyeth-Ayerst Laboratories *Philadelphia, PA*	interleukin	infectious diseases (see also cancer)	Phase I/II
Rotashield™ rotavirus vaccine, live, oral, tetravalent	Wyeth-Lederle Vaccines & Pediatrics *Philadelphia, PA*	continuous cell line vaccine	prevention of rotaviral gastroenteritis in infants	application submitted
rotavirus vaccine	Virus Research Institute *Cambridge, MA*	vaccine	rotavirus in infants	Phase II
Savvy™ C31G	Biosyn *Philadelphia, PA*	microbicide	infectious disease	Phase I
Tenefuse® lenercept (TNF-receptor fusion protein)	Hoffmann-La Roche *Nutley, NJ*	recombinant soluble receptor	septic shock, severe sepsis	Phase III
tifacogin	Chiron *Emeryville, CA* Searle *Skokie, IL*	tissue factor pathway inhibitor	sepsis	Phase II

TABLE A

INFERTILITY

Product Name	Company	Product Category	Indication	Development Status
Antide™ gonadotropin hormone-releasing hormone antagonist (GnRHA)	Ares-Serono and Serono Laboratories *Norwell, MA*	hormone-releasing hormone antagonist	female infertility	Phase I
Gonal-F® recombinant human follicle-stimulating hormone (r-FSH)	Serono Laboratories *Norwell, MA*	recombinant fertility hormone	male infertility	Phase III
LhADI® recombinant human leutinizing hormone (r-hLH)	Ares-Serono and Serono Laboratories *Norwell, MA*	recombinant fertility hormone	female infertility—follicular support, stimulation of follicular development	Phase II/III
Ovidrel® recombinant human chorionic gonadotropin (r-hCG)	Ares-Serono and Serono Laboratories *Norwell, MA*	recombinant gonadotropin	female infertility (see also AIDS/HIV)	Phase III

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Activase® alteplase, recombinant	Genentech *S. San Francisco, CA*	t-PA	acute ischemic stroke within 3 to 5 hours of symptom onset	Phase III
AnergiX™-MS	Anergen *Redwood City, CA*	functional antigenics immuno-therapy	multiple sclerosis	Phase I
Antegren natalizumab	Athena Neurosciences *S. San Francisco, CA*	MAb	multiple sclerosis flares	Phase II
ATM027 humanized MAb	T Cell Sciences *Needham, MA*	MAb	multiple sclerosis	Phase I
Avonex® interferon beta-1a	Biogen *Cambridge, MA*	interferon	secondary, progressive multiple sclerosis (see also cancer)	Phase III
Betaseron® recombinant interferon beta-1b	Berlex Laboratories *Wayne, NJ* Chiron *Emeryville, CA*	interferon	chronic progressive multiple sclerosis (see also cancer)	Phase III
brain-derived neurotrophic factor (BDNF)	Amgen *Thousand Oaks, CA* Regeneron Pharmaceuticals *Tarrytown, NY*	growth factor	amyotrophic lateral sclerosis	Phase I

TABLE A

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
CPC-211	Cypros Pharmaceuticals *Carlsbad, CA*	cellular therapy	ischemic stroke, traumatic brain injury	Phase II
enlimomab (anti-ICAM-1 MAb)	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	MAb	stroke (see also other)	Phase II/III
FIBLAST® trafermin	Scios *Mountain View, CA* Wyeth-Ayerst Laboratories *Philadelphia, PA*	growth factor	stroke (see also heart)	Phase II/III
Hu23F2G MAb	ICOS *Bothell, WA*	MAb	multiple sclerosis, ischemic stroke (see also heart, other)	Phase II
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	multiple sclerosis (see also AIDS/HIV, autoimmune, digestive, heart, respiratory, skin)	Phase I
IR 208 therapeutic vaccine	Immune Response Corp. *Carlsbad, CA*	vaccine	multiple sclerosis	Phase I
LDP-01	LeukoSite *Cambridge, MA*	MAb	stroke (see also transplantation)	Phase I/II
MS-TCR	Connetics *Palo Alto, CA*	vaccine	multiple sclerosis	Phase I/II
Myotrophin® rhIGF-1	Cephalon *West Chester, PA*	growth factor	amyotrophic lateral sclerosis	application submitted
	Chiron *Emeryville, CA*		peripheral neuropathies	Phase II
NeuroCell™-FE (cellular transplantation therapy)	Diacrin *Charlestown, MA*	cellular therapy	focal epilepsy	Phase I
NeuroCell™-HD (cellular transplantation therapy)	Diacrin *Charlestown, MA* Genzyme Tissue Repair *Cambridge, MA*	cellular therapy	Huntington's disease	Phase I completed
NeuroCell™-PD (cellular transplantation therapy)	Diacrin *Charlestown, MA* Genzyme Tissue Repair *Cambridge, MA*	cellular therapy	Parkinson's disease	Phase II
neurotrophin-3	Amgen *Thousand Oaks, CA* Regeneron Pharmaceuticals *Tarrytown, NY*	growth factor	enteric neuropathies	Phase I/II
pimagedine	Alteon *Ramsey, NJ* Genentech *S. San Francisco, CA*		overt neuropathy (see also diabetes)	Phase III
prosaptide TX14(A)	Myelos Neurosciences *San Diego, CA*	growth factor	neuropathic pain and peripheral neuropathy	Phase II

TABLE A

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Rebif® recombinant interferon beta-1a	Serono Laboratories *Norwell, MA*	interferon	relapsing, remitting multiple sclerosis; transitional multiple sclerosis (see also cancer, infectious diseases)	application submitted
ReoPro® abciximab	Centocor *Malvern, PA* Eli Lilly *Indianapolis, IN*	MAb	stroke (see also heart)	Phase II
Spheramine™	Titan Pharmaceuticals *S. San Francisco, CA*	cellular therapy	Parkinson's disease	Phase I
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	tropical spastic paraparesis (model for multiple sclerosis) (see also cancer, eye, skin, transplantation)	Phase I/II

RESPIRATORY DISEASES

Product Name	Company	Product Category	Indication	Development Status
AAV CFTR gene therapy	Targeted Genetics *Seattle, WA*	gene therapy	sinusitis (see also genetic)	Phase I
acellular pertussis vaccine	Chiron *Emeryville, CA*	vaccine	pediatric pertussis (whooping cough)	application submitted
anti-IgE humanized MAb	Genentech *S. San Francisco, CA* Novartis Pharmaceuticals *East Hanover, NJ* Tanox Biosystems *Houston, TX*	MAb	allergic asthma	Phase III
			allergic rhinitis	Phase II
Influenza rHAO Vaccine influenza vaccine	Protein Sciences *Meriden, CT*	vaccine	prevention of influenza	Phase II
influenza virus vaccine (live, attenuated)	Aviron *Mountain View, CA*	vaccine	prevention of influenza	Phase III
interleukin-4 receptor	Immunex *Seattle, WA*	recombinant soluble receptor	asthma	Phase I
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	acute lung injury (see also AIDS/HIV, autoimmune, digestive, heart, neurologic, skin)	Phase I
lisofylline	Cell Therapeutics *Seattle, WA*		acute lung injury (see also other)	Phase II
NEUPOGEN® Filgrastim (rG-CSF)	Amgen *Thousand Oaks, CA*	colony stimulating factor	multilobar pneumonia, pneumonia sepsis (see also AIDS/HIV, cancer)	Phase III

TABLE A

RESPIRATORY DISEASES

Product Name	Company	Product Category	Indication	Development Status
Oxsodrol® rhCu2r super dismutase	Bio-Technology General *Iselin, NJ*	dismutase	bronchopulmonary dysplasia in premature infants	Phase III
parainfluenza type-3 vaccine (live, attenuated bovine)	Aviron *Mountain View, CA*	vaccine	prevention of parainfluenza type-3 infection (cause of croup in infants)	Phase II
PIV vaccine, live, attenuated	Wyeth-Lederle Vaccines & Pediatrics *Philadelphia, PA*	continuous cell line vaccine	prevention of parainfluenza virus-mediated lower respiratory disease in infants	Phase I
Quillimmune-P	Aquila Biopharmaceuticals *Worcester, MA*	vaccine	pneumococcal infections in the elderly	Phase II
recombinant platelet activating factor-acetylhydrolase (rPAF-AH)	ICOS *Bothell, WA*		acute respiratory distress syndrome, asthma (see also digestive)	Phase II
RSV subunit vaccine	Wyeth-Lederle Vaccines & Pediatrics *Philadelphia, PA*	continuous cell line vaccine	prevention of respiratory syncytial virus-mediated lower respiratory disease in the elderly and at-risk children	Phase II
RSV vaccine, live, attenuated	Wyeth-Lederle Vaccines & Pediatrics *Philadelphia, PA*	continuous cell line vaccine	prevention of respiratory syncytial virus-mediated lower respiratory disease in infants	Phase I
soluble ICAM-1 (BIRR4)	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	recombinant soluble receptor	prevention and/or treatment of rhinovirus-induced common cold	Phase II
Synagis™ MEDI-493 humanized RSV MAb	Medimmune *Gaithersburg, MD*	MAb	prevention of respiratory syncytial virus disease	application submitted
TP10	T Cell Sciences *Needham, MA*	recombinant soluble receptor	acute respiratory distress syndrome (see also heart, transplantation)	Phase II
truncated ICAM	Bayer *Berkeley, CA*	adhesion molecule	rhinovirus-associated exacerbations of asthma	Phase I

TABLE A

SKIN DISORDERS

Product Name	Company	Product Category	Indication	Development Status
anti-CD11a humanized MAb (hu1124)	Genentech *S. San Francisco, CA* XOMA *Berkeley, CA*	MAb	moderate to severe psoriasis	Phase II
gamma interferon	Connetics *Palo Alto, CA*	interferon	keloids	Phase II
ICM3	ICOS *Bothell, WA*	MAb	psoriasis	Phase I
IL-2 fusion protein DAB_{389}IL-2	Seragen *Hopkinton, MA*	fusion protein	moderate to severe psoriasis (see also autoimmune, cancer)	Phase I/II
interleukin-10 (IL-10)	Schering-Plough *Madison, NJ*	interleukin	psoriasis (see also AIDS/HIV, autoimmune, digestive, heart, neurologic, respiratory)	Phase I
IR 502 therapeutic vaccine	Immune Response Corp. *Carlsbad, CA*	vaccine	psoriasis	Phase II
ISIS 2302	Isis Pharmaceuticals *Carlsbad, CA*	antisense	psoriasis (see also autoimmune, digestive, transplantation)	Phase II
keratinocyte growth factor-2 (KGF-2)	Human Genome Sciences *Rockville, MD*	growth factor	wound healing (see also other)	Phase I
LFA3TIP	Biogen *Cambridge, MA*	recombinant T-cell inhibitor	psoriasis	Phase II
Regranex™ becaplermin (recombinant human platelet-derived gr wth factor-BB)	Chiron *Emeryville, CA* R.W. Johnson Pharmaceutical Research Institute *Raritan, NJ*	growth factor	pressure ulcers (see also other)	Phase III
T4N5 Liposome Lotion T4 endonuclease V encapsulated in liposomes	Applied Genetics *Freeport, NY*		protection against actinic keratoses in patients with xeroderma pigmentosa	Phase III
TGF-beta3	OSI Pharmaceuticals *Uniondale, NY*	growth factor	impaired wound healing (see also other)	Phase II
transforming growth factor-beta-3	Novartis Pharmaceuticals *East Hanover, NJ*	growth factor	wound healing	Phase II
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	psoriasis (see also cancer, eye, neurologic, transplantation)	Phase I/II

TABLE A

TRANSPLANTATION

Product Name	Company	Product Category	Indication	Development Status
allogeneic hematopoietic stem cells	SyStemix *Palo Alto, CA*	cellular therapy	correct genetic diseases by in utero transplantation of genetically unaffected cells from a sibling or parent	Phase I
CBL antibody (ABX-CBL)	Abgenix *Foster City, CA*	MAb	graft versus host disease	Phase II
CTLA4Ig	Bristol-Myers Squibb *Princeton, NJ*	recombinant soluble receptor	immunosuppression	Phase II
HSD-Tk retroviral vector	Genetic Therapy *Gaithersburg, MD* SyStemix *Palo Alto, CA*	gene therapy	treatment of graft versus host disease in allogeneic hematopoietic stem cell transplantation	Phase I
HSV-tk	Chiron *Emeryville, CA*	gene therapy	graft versus host disease in bone marrow transplantation	Phase I
ISIS 2302	Isis Pharmaceuticals *Carlsbad, CA*	antisense	renal transplant rejection (see also autoimmune, digestive, skin)	Phase II
LDP-01	LeukoSite *Cambridge, MA*	MAb	kidney transplantation (see also neurologic)	Phase I/II
MEDI-507 (humanized MAb)	MedImmune *Gaithersburg, MD* BioTransplant *Charlestown, MA*	MAb	graft versus host disease	Phase II
			acute kidney transplant rejection	Phase I/II
ORTHOCLONE OKT4A	Ortho Biotech *Raritan, NJ*	MAb	prevention of organ transplant rejection (see also autoimmune)	Phase II
Simulect basiliximab	Novartis Pharmaceuticals *East Hanover, NJ*	MAb	transplantation	application submitted
SMART™ Anti-CD3 HuM291	Protein Design Labs *Mountain View, CA*	MAb	organ transplantation (see also autoimmune)	Phase I
TP10	T Cell Sciences *Needham, MA*	recombinant soluble receptor	transplantation (see also heart, respiratory)	Phase I/II
Zenapax® daclizumab	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	liver transplantation (see also cancer, eye, neurologic, skin)	Phase II
			pediatric kidney transplantation	Phase I/II
Zenapax® daclizumab and Cellcept®	Hoffmann-La Roche *Nutley, NJ* Protein Design Labs *Mountain View, CA*	MAb	kidney transplant rejection, cyclosporine elimination	Phase I/II

TABLE A

OTHER

Product Name	Company	Product Category	Indication	Development Status
Recombumin recombinant human albumin	Centeon *King of Prussia, PA*		excipient use	Phase I
Regranex™ becaplermin (recombinant human platelet-derived growth factor-BB)	Chiron *Emeryville, CA* R.W. Johnson Pharmaceutical Research Institute *Raritan, NJ*	growth factor	venous ulcers (see also skin)	Phase III
rhBMP-2	Genetics Institute *Cambridge, MA*	growth factor	bone and cartilage repair	in clinical trials
Saizen® somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	chronic renal failure in children (see also growth disorders)	Phase III
			post-operative recovery	Phase II
Serostim™ somatropin (rDNA origin) for injection	Serono Laboratories *Norwell, MA*	human growth hormone	metabolic conditions (see also cancer)	Phase II
Somatokine® recombinant insulin-like growth factor-I/ binding protein-3	Celtrix Pharmaceuticals *Santa Clara, CA*	growth factor	hip fractures, severe acute burns	Phase II
TGF-beta3	OSI Pharmaceuticals *Uniondale, NY*	growth factor	oral mucositis (see also skin)	Phase II

The content of this survey has been obtained through government and industry sources based on the latest information. Survey current as of March 13, 1998. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly.

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In one aspect, particular benefit is obtained with this invention when used with biopharmaceuticals, which include, for example, any proteins, polypeptides, enzymes, immunoglobulins, polynucleic acids, and plasmids or other biopolymers. Specific examples of biopharmaceuticals to be included in the crystal formulations of the present invention include the following: insulin, glucagon, Glucagon-Like Peptide-1 (7-37)OH (GLP-1), human growth hormone, leptin, follicle-stimulating hormone (FSH), ribozyme, and analogs thereof .

The API's useful with the present invention include those which themselves may form crystalline products, as well as those which do not. By way of example, any proteins can be prepared as microcrystalline suspension products, but the results have frequently been unsatisfactory using existing technology. However, inclusion of these biomolecules into a host crystal system in accordance with the present invention overcomes this limitation on crystallization. The invention further finds utility even with API's that are readily crystallized, such as insulin. The incorporation of such API's into a single crystal lattice can be used to enhance stability or provide means of delivery that have different characteristics.

Solvents for preparation of the saturated and supersaturated crystal lattice component include, but are not limited to, water, alcohols (e.g., ethanol, isopropanol), other organic solvents, acids, bases, and buffers.

The crystals of the present invention are prepared to have a predetermined amount of active pharmaceutical ingredient. The desired amount of active pharmaceutical ingredient will depend on typical considerations, such as the effective amount of API used for administering to a patient. The concentration of API in the crystal is controlled, such as by previously described means, to yield crystals which are readily used in preparing pharmaceutical formulations for administration. The active pharmaceutical ingredient can be incorporated into the crystals at any of a wide variety of molar or weight percentages. Preferred percentages can be easily selected by a skilled artisan taking into account the usual considerations for later formulation of the desired pharmaceutical compositions, depending on the application, route of delivery, and desired pharmacological profile. Preferred percentages include, for example, concentrations of 0.01 - 1 weight percent. As used herein, all weight percentages are given as the percent

based on the weight of the crystal including the crystal lattice component, the active pharmaceutical ingredient and any other components included within the crystals, unless stated otherwise.

The crystals may be prepared at varying size distributions, similarly depending on the subsequent formulating to be done with the crystals, or on crystal growth parameters. The crystals may be harvested and then sorted directly to desired size ranges, or may first be processed, such as by grinding or milling, and then sorted such as by sieving. As will be appreciated, a desired amount of active pharmaceutical ingredient may be obtained simply by obtaining a determined weight of crystals containing the active pharmaceutical ingredient at a known weight concentration. The useful size or weight range of the crystals of the present invention accordingly varies widely, depending on such factors as the inclusion level of the active pharmaceutical ingredient, the dosage amount for the active pharmaceutical ingredient, and the method of delivery of the crystals. By way of example, suitable crystals may have an average size distribution of 1 μm to 1 mm .

The crystals of the present invention will typically be used in a formulation comprising a large number of crystals. It is a feature of the present invention that the active pharmaceutical ingredient is included within the crystal lattice component in a predictable, oriented fashion. This leads to a uniform concentration of the active pharmaceutical ingredient as a molar, and therefore weight, percentage of the crystals. In one aspect of the present invention, there is provided a composition of crystals having a substantially uniform weight concentration of active pharmaceutical ingredient as between crystals. The term "substantially uniform weight concentration" refers to the fact that the weight concentration of active pharmaceutical ingredient in the various crystals is sufficiently uniform that an acceptably accurate weight of active pharmaceutical ingredient can be obtained based on the weight of the crystals and the average concentration of active pharmaceutical ingredient in such crystals. In one preferred embodiment, there is provided a composition of crystals in which the size distribution of active pharmaceutical ingredient does not vary between crystals by more than about 20 percent. However, alternate embodiments may be equally

useful, including mixtures of different size crystals. A desired quantity of active pharmaceutical ingredient is then accurately obtained by measuring a weight amount of crystals which, given the concentration of active pharmaceutical ingredient, yields the selected weight of active pharmaceutical ingredient.

The crystals and included API's are useful in the crystal form for both the stabilization and storage of the API and for the administration of the API to a patient. As used herein, it will be appreciated that the term patient refers to either humans or non-humans, depending on the nature of the active pharmaceutical ingredient. The crystals may be used as such, and in one aspect of the present invention the crystals consist essentially of simply the crystal lattice component and the API. Alternatively, the crystals include the crystal lattice component and the API in combination with other pharmaceutically-acceptable adjuvants also contained within the crystals.

The crystals of the present invention are preferably formulated as pharmaceutical materials for ultimate delivery in solid or liquid form. In such applications, the crystals are typically formulated with common, compatible, pharmaceutically-acceptable adjuvants, such as excipients, diluents, carriers or mixtures thereof. For purposes herein, the term "pharmaceutically-acceptable" refers in this context to the excipients, diluents or carriers, as well as coatings or other components referred to elsewhere, being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Examples of excipients, diluents, and carriers that are suitable for such dosage forms are well known in the art, and include the following: suspension additives such as tonicity modifiers, buffers, precipitants, and preservatives; fillers and extenders such as starch, lactose, dextrose, sucrose, sorbitol, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol and glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid

polyethyl glycols. Additionally, the adjuvant may comprise crystals of the crystal lattice component that are prepared without the included API.

The crystals may be coated to achieve various effects. In one approach, the crystals are coated with the same crystal lattice component which forms the underlying crystal, but without the included API. This assures that the coating and the underlying crystal have compatibility. The coating is then applied at a thickness which provides the desired effect, such as further protection of the active pharmaceutical ingredient, bulking of the crystal for handling, and/or effecting a sustained or delayed release of the active pharmaceutical ingredient. Alternatively, the same effects can be accomplished by coating the crystals with other compatible coating compositions, such as those which are well known in the pharmaceutical coating art. The crystals can also be coated so as to release the active pharmaceutical ingredient only or preferably in a particular part of the intestinal tract or other route of administration, possibly over a period of time. This is accomplished, in known fashion, using coatings, envelopes, and protective matrices made, for example, from polymeric substances or waxes.

It is a feature of one aspect of the present invention that the crystals and included API's may be packaged and administered to patients in discrete pharmaceutical dosage forms. The crystals may be used as such in solid form, or may be formulated into liquid solutions or suspensions prior to use. The compositions may accordingly be administered by various routes, for example, by the oral, rectal, vaginal, ocular, buccal, nasal, pulmonary, iontophoretic, topical or parenteral routes. Such compositions form part of the present invention and are prepared in manners well known in the pharmaceutical art.

The API's of the present invention are effective over a varied dosage range. Such dosages are readily accommodated by the present invention by permitting various sizes of crystals, concentrations of API, etc. It will be understood that the amount administered will be determined in light of the relevant circumstances, including the condition to be treated, the choice of API to be administered, the size of the patient being treated, and the chosen route of administration. Therefore, specific dosage ranges will differ accordingly, and are not limiting of the scope of the invention in any way.

The compositions are formulated in one embodiment as a unit dosage form. The term "unit dosage form" refers to physically discrete units, such as tablets, capsules, and suspensions in vials or cartridge/pen systems suitable as unitary dosages, particularly as unitary daily dosages. Each discrete unit contains a predetermined quantity of active pharmaceutical material calculated to produce the desired effect, e.g., a prophylactic or therapeutic effect. The amount of active pharmaceutical ingredient contained in a given dosage unit can be varied depending on the manner of delivering the crystals. For example, a single dosage unit in tablet form may contain 1/4, 1/3, 1/2 or 1 times the unit dose for the active pharmaceutical ingredient, according to which 1 to 4 tablets would be administered to achieve a unit dose of the active pharmaceutical ingredient.

Therefore, in one aspect of the present invention, there is provided a pharmaceutical product in dosage form comprising a pharmaceutical delivery unit including a dosage amount of active pharmaceutical ingredient. The API is contained within the crystal lattice component, and a sufficient amount of crystals is included within the delivery unit to constitute the dosage amount of the API. It will be appreciated that the dosage amount of pharmaceutical may be obtained by provision of one or more crystals of the present invention. One form of the product consists essentially of a dosage amount of the crystals. In an alternative form, the pharmaceutical product consists of the dosage amount of the crystals.

The ultimate delivery forms may include, for example, tablets, soft and hard gelatin capsules, pellets, granules, marumes, lozenges, sachets, cachets, elixirs, suspensions, ointments, suppositories, injection solutions and suspensions, nonpareils, spheres and sterile packaged powders. The crystals may be coated or uncoated, and may be combined with various pharmaceutical adjuvants, including excipients, diluents and carriers, as already described. One preferred form of the pharmaceutical product consists essentially of the crystals, and an alternate form consists of the crystals and the pharmaceutically-acceptable adjuvants. The delivery forms are prepared by conventional techniques such as disclosed in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, Easton, PA (1995), which is incorporated herein by reference, or other treatises available to the skilled artisan.

Compressed tablets, for example, are prepared by well-known means which are conventional in the art. The tablets may be prepared by wet or dry granulation methods or by direct compression, and may be produced by any of a wide variety of tabletting machines. Tablet formulations usually incorporate diluents, binders, lubricants and disintegrators, as well as the crystals with included API's. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride, and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin, and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

Certain solid pharmaceutical dosage forms of the present invention, most notably tablets, may be coated in conventional fashion with a wide variety of materials utilizing various processes. Typically, the products of the present invention may be sugar coated or film coated in accordance with well-known techniques. The coatings serve an aesthetic purpose as well as a practical one. Coatings can mask an unpleasant taste or odor, can increase ease of ingestion by the patient, and can serve to improve the ultimate appearance of the dosage form. Similarly, coatings can protect the product from the effects of air, moisture and light, can improve product identification, and can facilitate handling in packaging and fill lines during manufacture.

Various adjuvants may be included in the coating formulations as is well known in the art. These include, for example, permeability enhancers, plasticizers, antitacking agents and the like. A discussion of coating techniques and adjuvants is presented in United States Patent No. 5,015,480, issued to Childers et al. on May 14, 1991, the pertinent portions of which are hereby incorporated herein by reference. Further information pertinent to coating processes and equipment may be obtained from Remington's Pharmaceutical Sciences, supra.

Tablets are often coated with sugar as a flavorant and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets by using large amounts of

pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the subject consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some subjects.

A lubricant is used in a tablet formulation to prevent the tablet and punches from sticking in the die of the tabletting machine. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the crystals. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are used to protect crystals and the included API's from the strongly acidic contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acidic environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

The crystals with included API's may similarly be formulated into capsules for administration. Such capsules are prepared utilizing conventional encapsulating methods. A general method of manufacture involves preparing the crystals for use in capsules, such as by milling the crystals to a suitable size. The crystals are blended with desired excipients, diluents or carriers, and the resulting mixture is filled into suitably-sized capsules, typically hard gelatin capsules, using conventional capsule-filling machines. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

When it is desired to administer the crystal formulations as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which

may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are also in wide use.

The crystals can also be similarly formulated as elixirs or suspensions for convenient oral administration or for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes.

The inventive crystals enable the design of sustained-release formulations based upon various factors to yield both the desired amount of active pharmaceutical ingredient and the desired pharmacokinetic profile for delivery of the active pharmaceutical ingredient. Selectively incorporating the active pharmaceutical ingredient into the crystal lattice, e.g., into a specific crystal growth sector, modulates the release profiles and can therefore be used to effect desired pharmacological properties. The choice of the crystal component and the process used to grow the crystals of excipient host and guest active pharmaceutical ingredient can be selected and/or modified to adjust parameters such as the delivery rate of the active pharmaceutical ingredient upon use of the formulation. The active pharmaceutical ingredient is incorporated into the crystal matrix at a selected rate, typically as only a small weight percentage of the overall crystal. This permits moderate and uniform rates of release.

Various approaches may be used to accomplish a delayed or sustained release of active pharmaceutical ingredient from the crystals. In a typical application the crystals of the desired size are combined with a compatible preservative and the mixture is injected subcutaneously or surgically implanted to provide a prolonged payout as the crystals dissolve as a result of contact with the surrounding body tissue and fluid. In one approach, the concentration of the active pharmaceutical ingredient in the crystals is reduced in order to effect a sustained release over time. Alternatively, larger crystals may be used to provide for more prolonged payout of the active pharmaceutical ingredient. In another approach, coatings on the crystals are used to affect the rate of release of the active pharmaceutical ingredient. Such coatings may comprise the same crystal lattice component but without the included active pharmaceutical ingredient, as well as other coating compositions useful for this purpose.

In the alternative, the crystals of the present invention can be used to isolate and/or store the active pharmaceutical ingredient for later reconstitution into solution. The crystals may be stored for extended periods of time prior to reconstitution in view of the added stability accorded the API's by the encompassing crystal lattice component. The crystals are then combined with pharmaceutically-acceptable excipients, diluents or carriers to prepare the solutions for subsequent administration. The crystals are readily dissolved or suspended in appropriate diluents, which may be selected, for example, from the list previously provided with regard to diluents used to initially prepare the crystals.

Such solutions of dissolved crystals provide the active pharmaceutical ingredient free of the previously encompassing crystal lattice component. The solutions are useful, for example, for oral administration, parenteral use, or as suppositories. For parenteral administration, for example, the crystals may be formulated in a pharmaceutically-acceptable diluent such as physiological saline (0.9%), 5% dextrose, Ringer's solution, and the like, along with other additives to reduce the solubility of the crystals in suspension.

The resulting pharmaceutical formulations provide an active pharmaceutical ingredient which is included within the host crystal and has enhanced stability and shelf-life. The present invention therefore satisfies the desire to provide certain pharmaceuticals having an acceptable, room-temperature shelf-life. Depending on the circumstances, particularly the API involved, the desired shelf-life can be as little as one month, or may be at least one year, two years or more. The pharmaceutical molecules are generally isolated from one another and from the environment by the surrounding crystal lattice. The containment of the API in the solid crystal lattice also fixes the conformational orientation. This eliminates most of the potential degradation mechanisms, such as polymerization, oxidation, deamidation and proteolysis, that could otherwise reduce the stability of the pharmaceutical.

Methods demonstrating stability include but are not limited to high-performance liquid chromatography for purity and potency, FT-IR for secondary structure, in-vitro and in-vivo bioassays, and pharmacokinetic profiles.

The crystals of the present invention are readily prepared and are useful in containing the included API in an isolated, oriented position within the lattice. The utility of the present invention is demonstrated in the following examples, which are illustrative in nature, and are not to be considered limiting of the scope of the present invention.

Example 1

To demonstrate the potential kinetic stabilization of proteins, green fluorescent protein (GFP) was incorporated into deionized α-lactose monohydrate. GFP was selected because it is known to fluoresce only in its native conformation. Upon denaturation, the interior of the β-barrel of the molecule is exposed and the fluorescence of the p-hydroxybenzylideneimidazolinone chromophore is rapidly quenched. Typical crystal growth conditions involved the addition of 8 volumes of an approximately 1 mg/mL (approximately 37 μmole) solution of GFP in 10 mM tris-HCl, pH8 and 10 mM EDTA to 100 volumes of a supersaturated aqueous solution (approximately 1.15 M) of deionized α-lactose monohydrate. The mixed solution was allowed to stand for 3-4 days at room temperature in a 24-well plate. Crystals were harvested between 1-3 days and displayed a hatchet morphology as shown in Figure 1 with a broad base (010) further bounded by {100}, {110}, {1-10}, and {0-11}. Small (0-10) and {1-50} faces are also occasionally present. When illuminated with a long wavelength UV lamp, the crystals exhibited a bright green fluorescence localized within a sharply defined pyramid corresponding to the (010) growth sector. This indicates that GFP is selectively recognized and overgrown by the (010) face in preference to the others. More importantly, it is evidence that the GFP is in its native conformation. The level of GFP to lactose is approximately 0.008% (w/w).

GFP fluorescence intensity was measured as a function of time and temperature in three environments: saturated aqueous α-lactose solution, lyophilized α-lactose, and crystalline α-lactose monohydrate. As shown in Figure 2, both the solution and lyophilized preparations lost nearly half of the fluorescence intensity at 333°K within one hour. The crystal showed no change at 333°K or even 343°K.

Example 2

To investigate the potential for incorporation of a biopharmaceutical into crystals of biocompatible excipients, studies were conducted using rhodamine-labeled glandular glucagon and lactose. As in the previous studies, the rhodamine label was used to facilitate the visualization of glucagon in the host crystals. Typical crystal growth conditions involved the addition of 5 volumes of a supersaturated solution of deionized α-lactose monohydrate to 1 volume of an approximately 1.5 mg/mL (approximately 300 to 400 μmole) of rhodamine-labeled glucagon in purified water. The mixed solution was allowed to stand at room temperature in a 24-well plate. Crystals were harvested between 1-3 days and displayed a hatchet morphology with a broad base. With the rhodamine label, glucagon inclusion was visible in the crystals as a well-defined pyramid corresponding to the (010) growth sector. The level of inclusion was determined to be approximately 0.1% (w/w).

In-vitro dissolution experiments were performed on the glucagon/lactose crystals to evaluate potential for in-vivo, sustained-release pharmacokinetics. The release of rhodamine-labeled glucagon into solution was followed by fluorescence spectroscopy. In a typical experiment, 1-2 crystals were added to 100 microliters of phophate buffered saline solution at room temperature and the increase in fluorescence of the solution was monitored over time. The release of glucagon from the dissolving crystals was generally complete after 24-48 hours depending on crystal size and was linear until the last few hours of dissolution. Additional details are contained in the article entitled "Stabilization of Proteins in Single Crystal Hosts: Green Fluorescent Protein and α-Lactose Monohydrate," M. Kurimoto, P. Subramony, R. Gurney, S. Lovell, J.A. Chmielewski, B. Kahr, J. Am. Chem. Soc. 1999, 121, 6952-6953, which article is hereby incorporated herein by reference.

Example 3

To demonstrate the universality of this technology for incorporation of a diversity of biopharmaceuticals into crystals of biocompatible excipients, studies were conducted using biosynthetic human insulin and insulin analogs,

V8-GLP-1(7-37)OH, a glucagon-like insulinotropic peptide-1 analog, exendin, and human growth hormone in deionized α-lactose monohydrate or phthalic acid. Information regarding V8-GLP is available in United States Patent No. 5,705,483, issued to Galloway and Hoffman on January 6, 1998, which patent is hereby incorporated herein in its entirety. For information regarding exendin, see, e.g., R. Goke, H.C. Fehmann, T. Linn, H. Schmidt, M. Krause, J. Eng, B. Goke, "Exendin-4 is a High Potency Agonist and Truncated Exendin-(9-39)-amide an Antagonist at the Glucagon-like Peptide 1-(7-36)-amide Receptor of Insulin-secreting Beta-cells," J. Biol. Chem. 1993, Sep 15, 268(26), pp. 19650-5, which reference is hereby incorporated herein in its entirety.

Typical crystal growth conditions involved the addition of 1 volume of an approximately 10 mg/mL rhodamine- or Texas red-labeled peptide or protein in 0.1M phosphate-buffered saline solution (PBS, pH7.4) to 10 volumes of a supersaturated α-lactose solution or phthalic acid solution. Supersaturated solutions of purified α-lactose were obtained by adding 0.41 grams of α-lactose to 1 mL of purified water, allowing to dissolve in a 50-70°C water bath, and cooling to room temperature. Supersaturated solutions of phthalic acid were prepared by adding 0.05 grams of phthalic acid to 1 mL of either 70/30 (v/v) water/acetonitrile or 90/10 water/ethanol, allowing to dissolve in a 50-70°C water bath, and cooling to room temperature. Larger volumes of supersaturated solutions are obtained by using the same solute-to-solvent ratio.

The solutions of labeled peptide or protein with the supersaturated α-lactose or phthalic acid were mixed by swirling, transferred to a 24-well crystallization plate or other suitable glass or polypropylene container, and allowed to stand at room temperature. Crystals were harvested in 4-5 days and rinsed with hexanes, ethanol, or methanol. All preparations yielded crystals with dye-labeled protein inclusions as determined by microscopic examination using an Olympus SZ-40 microscope with a CCD vision camera.

The shape of the crystals formed was dependent on the solvent system used for the phthalic acid. The crystals formed with phthalic acid in water/ethanol were long, petal-shaped clusters. The crystals formed with water/ethanol were smaller

and rhombic. Crystals of labeled-insulin/lactose were dissolved in PBS and analyzed by HPLC. The level of insulin inclusion was determined to be approximately 0.1%. This process is scalable from 100 μL to several liters. The larger volume crystallizations were performed using glass beakers, or other appropriate large containers, covered with watch glasses.

Using the same process, unlabeled insulin and exendin have also been incorporated into α-lactose monohydrate and phthalic acid crystals. Upon dissolution of the crystals with 0.01N HCl, purified water and/or methanol, the level of peptide included in these hosts was determined by analysis of the sample solutions with an HPLC system in the flow-injection analysis mode using a chemiluminescent nitrogen-specific detector (CLND). The level of peptide inclusions ranged from approximately 0.1% to 10% (w/w). These data demonstrate that the level of inclusion can be manipulated by appropriate choice of guest and host molecules in addition to crystallization conditions. See also the following references which are hereby incorporated herein in their entirety: M. Windholz, (editor). Merck Index, 10th edition, p. 769; R.A. Visser, Neth. Milk Dairy Journal, **34**, 1980, pp. 255-275; J. Chmielewski, et al., JACS, **119**, 43, pp. 105665-10566.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a single crystal of a pharmaceutically-acceptable crystal lattice component; and

an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

2. A pharmaceutical material comprising:

a mixture of single crystals, each crystal comprising a pharmaceutically-acceptable crystal lattice component and an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

3. The pharmaceutical material of claim 2 in which the crystals comprise at least two crystal lattice components, the first crystal lattice component being characterized by first pharmacokinetics and the second crystal lattice component being characterized by second pharmacokinetics.

4. The pharmaceutical material of claim 2 in which said mixture comprises a mixture of two different types of said crystals, the first type of the crystals comprising a first crystal lattice component and the second type of the crystals comprising at least one crystal lattice component different from the first crystal lattice component.

5. The pharmaceutical material of any of claims 2 to 4 in which the active pharmaceutical ingredient comprises discrete units and the units are included within the crystals in isolation from one another.

6. The pharmaceutical material of any of claims 2 to 5 in which the active pharmaceutical ingredient is included within the crystal at a concentration of about 0.001 to 1 weight percent based on the weight of the crystal including the active pharmaceutical ingredient.

7. A method of preparing a pharmaceutical product which comprises:

including an active pharmaceutical ingredient into single crystals of a pharmaceutically-acceptable crystal lattice component, the including being

conducted under pharmaceutically-acceptable conditions to provide the active pharmaceutical ingredient in the crystals in a growth-sector specific orientation; and

harvesting the single crystals.

8. The method of claim 7 and which further includes dissolving the harvested crystals into a pharmaceutically-acceptable diluent to form a solution containing the pharmaceutical free of the crystals.

9. A method of stabilizing an active pharmaceutical ingredient which comprises including the active pharmaceutical ingredient into single crystals of a pharmaceutically-acceptable crystal lattice component, the including being conducted under pharmaceutically-acceptable conditions to provide the active pharmaceutical ingredient in the crystals in a growth-sector specific orientation, the active pharmaceutical ingredient comprising discrete units and the units being included in the crystals in isolation from one another.

10. A method of administering an active pharmaceutical ingredient which comprises administering to a patient a pharmaceutical composition comprising single crystals of a pharmaceutically-acceptable crystal lattice component and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

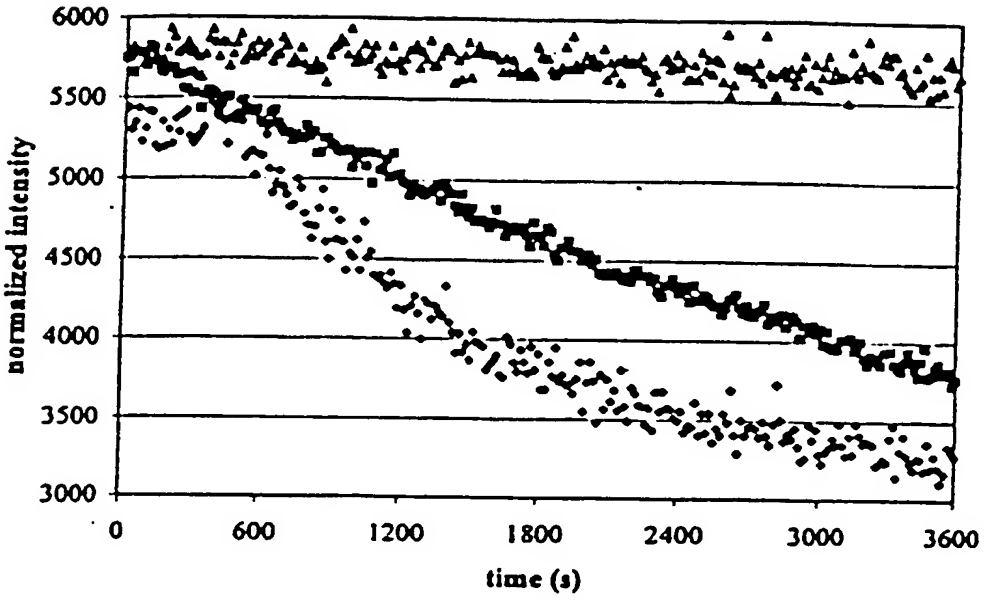
11. The invention of any of claims 1 to 10 in which, for each crystal, the active pharmaceutical ingredient is included within the crystal in a growth-sector specific orientation.

12. The invention of any of claims 1 to 11 and further comprising a pharmaceutically-acceptable adjuvant selected from the group consisting of excipients, diluents, carriers and mixtures thereof.

13. The invention of any of claims 1 to 12 in which the active pharmaceutical ingredient is a biopharmaceutical.

14. The invention of any of claims 1 to 13 in which the crystal lattice component is selected from the group consisting of: sucrose, lactose, trehalose, maltose, galactose, sorbose, mannitol, lactitol, sorbitol, glycine, alanine, lysine,

arginine, ascorbic acid, nicotinamide, thiamine, adenine, pyridoxine hydrochloride, caffeic acid, vanillic acid, ferulic acid, benzoate, sorbate, methyl paraben, sodium ascorbate, sodium saccharin, potassium citrate, zinc, calcium, and any derivatives, salt forms, or mixtures thereof.


6000
5500
5000
4500
4000
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3000
normalized intensity
0
600
1200
1800
2400
3000
3600
time (s)

FIG. 1

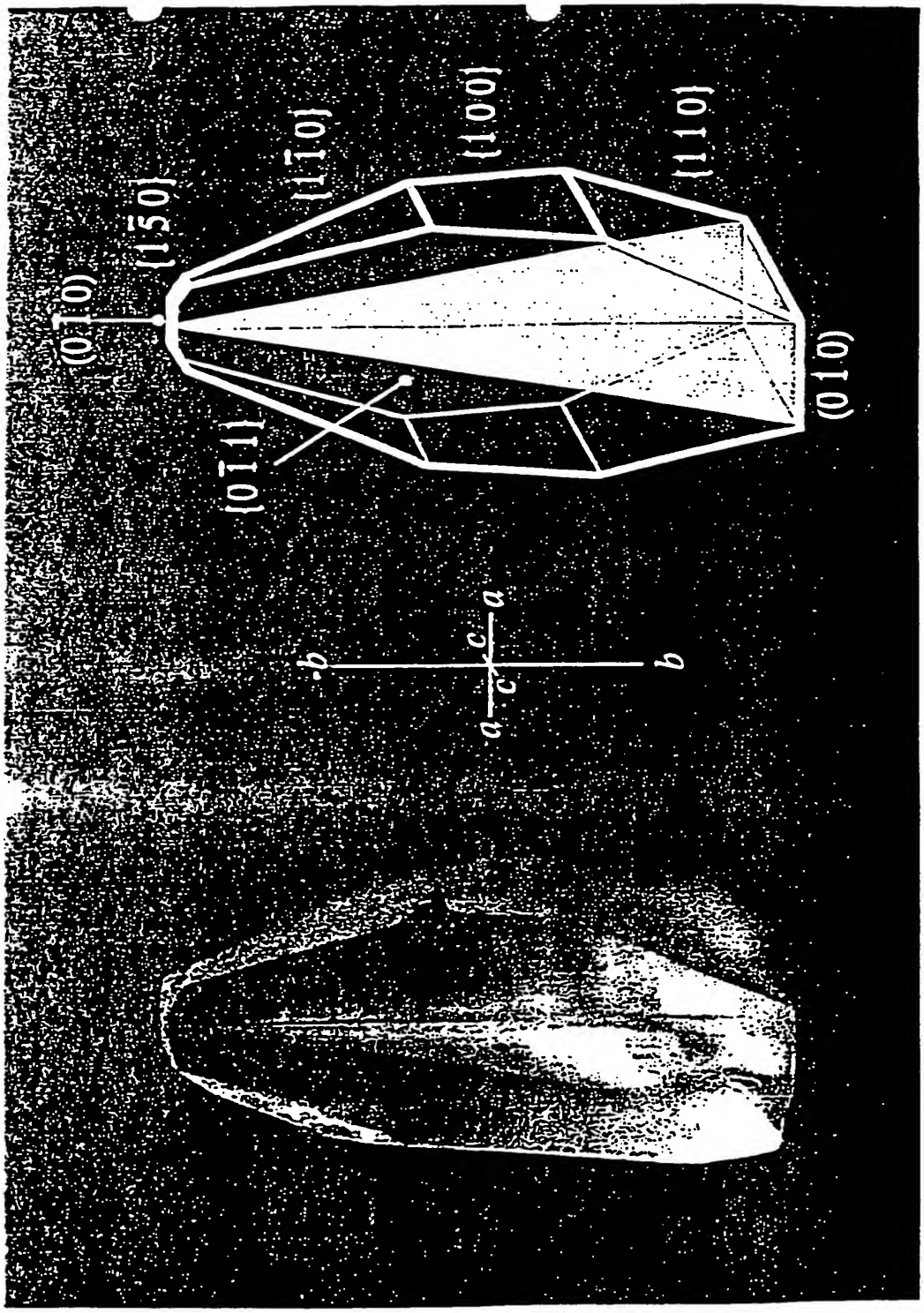

FIG. 2

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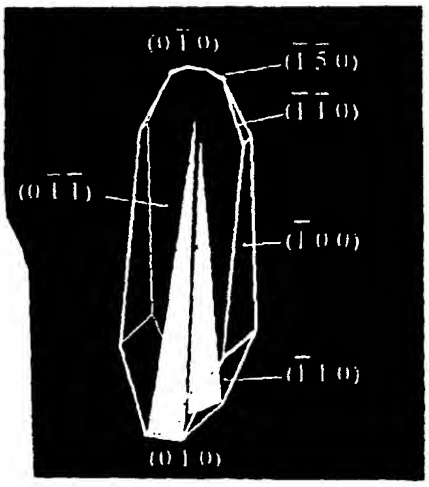
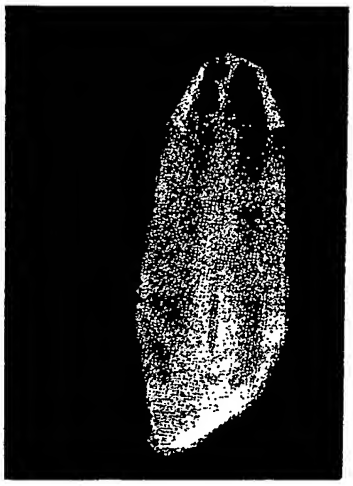
(54) Title: PHARMACEUTICAL MATERIALS AND METHODS FOR THEIR PREPARATION AND USE





(57) Abstract: Pharmaceutical compositions comprising crystals of a pharmaceutically-acceptable crystal lattice component, and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation. The crystals are prepared using components and methods which yield crystals having suitable purity and efficacy for use in administering the active pharmaceutical ingredients to a patient. The crystals are typically combined with adjuvants such as excipients, diluents or carriers, and are preferably formulated into tablets, capsules, suspensions, and other conventional forms containing predetermined amounts of the pharmaceuticals. Also provided are methods for preparing the crystals, and methods for storing and administering the active pharmaceutical ingredient either included within the crystals or upon reconstitution of the crystals to a solution.

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IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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PHARMACEUTICAL MATERIALS AND METHODS FOR THEIR PREPARATION AND USE

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to pharmaceutical formulations involving the inclusion of an active pharmaceutical ingredient ("API") in a pharmaceutically-acceptable single crystal matrix. More particularly, the crystals contain growth-sector specific, oriented inclusions of active pharmaceutical ingredients which are isolated. The active pharmaceutical ingredients have higher stability and shelf-life, and can be delivered in conventional dosage forms. This invention has general application to active pharmaceutical ingredients, and in one aspect has particular application to biopharmaceuticals. As used herein, the term "biopharmaceuticals" is used to refer to a subset of API's which are polymeric in nature, including for example, proteins, polypeptides, enzymes, immunoglobulins, polynucleic acids, and plasmids.

Description of the Prior Art:

There is a continuing need for pharmaceutical compositions which are capable of maintaining the quality and efficacy of the API during storage and delivery. The loss of potency of an API is a critical concern in assuring that viable, effective drugs are delivered to patients. It is similarly desirable to have formulations which do not require special packaging or handling. Further, it remains a constant goal to provide active pharmaceutical ingredients in a form which facilitates their use by the consumer, such as through convenient dosage forms. The present invention addresses these and other issues concerning pharmaceutical compositions and formulations.

Although not limited to biopharmaceuticals, the usefulness of the present invention is well exemplified with respect to biopharmaceuticals, many of which demonstrate the problems encountered in prior-art approaches. Ensuring long-term stability and maintaining activity of biopharmaceuticals is a prevalent concern. The chemical complexity and conformational fragility of protein drugs, for example, make them highly susceptible to both physical and chemical instabilities

and threaten their emergence into the marketplace. Denaturation, adsorption with container walls, aggregation, and precipitation can result from non-covalent interactions between a drug and its environment. Insulin, for instance, has been shown to adsorb onto the surfaces of glass and plastic containers, and to have interactions at air-water interfaces, leading to denaturation, aggregation and precipitation. For example, upon denaturation human growth hormone (HGH) forms dimers and higher molecular weight aggregates, and glucagon in solution has been shown to readily gel or aggregate when subjected to mechanical stress.

As a further example, researchers have distinguished nine major reaction mechanisms by which proteins degrade, including hydrolysis, imide formation, deamidation, isomerization, racemization, diketopiperazine formation, oxidation, disulfide exchange, and photodecomposition. The rates of these deleterious processes depend in large measure on the protein and its environment. The primary chemical degradation products of glucagon, for example, include oxidation of Met (27), deamidation of Gln (24), and acid-catalyzed hydrolysis at Asp (9), Asp (15) and Asp (21). HGH undergoes chemical decomposition via oxidation at Met (14) and deamidation at Asn (149).

A critical challenge of product development science in the pharmaceutical industry therefore has been devising formulations that maintain the stability of the active pharmaceutical ingredient over an acceptable shelf-life. This has been especially difficult to achieve for certain API's which are unstable in solution or with respect to many common formulation processes. Developing techniques for stabilization and storage looms as a great impediment to the pharmaceutical industry. Formulation scientists have consequently used a variety of techniques to enhance the stability of API's while maintaining other important product characteristics such as biocompatibility, absorption, pharmacokinetics, efficacy and excretion.

One technique used in formulating biopharmaceuticals has been lyophilization of the biopharmaceutical solution in the presence of excipients, buffers and/or bulking agents. However, even lyophilized preparations must typically be stored under refrigeration, a requirement which is neither technically

nor economically feasible in many markets and inhibits flexibility of patient use. There has therefore been a continuing demand for formulations of many biopharmaceuticals which would permit their storage at ambient temperatures. This would permit more rapid development of products, increasing flexibility in shipping, storing and carrying the drug products, and allowing introduction and use of such products in markets where refrigeration is too costly. Moreover, the increased stabilization of biopharmaceuticals would naturally improve the general use of the biopharmaceuticals where shelf life is an important consideration, whether or not refrigeration or other concerns are at issue.

The prior art use of excipients in the lyophilization of biopharmaceuticals has been directed away from inclusion of the biopharmaceuticals in single crystals in the manner of the present invention. It has been widely assumed that amorphous glasses are critical in the stabilization of biopharmaceuticals by such excipients in lyophilized form, and it has been suggested that the drug molecules must exist in amorphous regions between the crystalline domains. See, e.g., M. J. Pikal, "Freeze Drying of Proteins", to be published in Peptide and Protein Delivery, 2nd Ed., V. H. L. Lee, Marcel Dekker, Preprint, 1995. Implicit in this reasoning is the conclusion that the biopharmaceuticals could not exist as guests within single crystals.

In the process of lyophilization, typically an aqueous solution containing a biopharmaceutical with a limited amount of excipient(s) is frozen and then dried under vacuum to produce solids of sufficient stability for storage and distribution. Excipients are added to prevent blow out of the product, to provide stability during lyophilization and/or dissolution, and to enhance compatibility for parenteral use. Various excipients used with lyophilization have included salts, metal ions, polyalcohols, surfactants, reducing agents, chelating agents, other proteins, amino acids, fatty acids, and phospholipids. The more frequently used excipients include mannitol, alanine, glycine, sorbitol, lactose, arginine, and maltose. The results obtained with such excipients, however, have usually been inconsistent. Most lyophilized biopharmaceuticals are amorphous powders that have no specific structure, and as a result, the amount and location of the incorporated biopharmaceutical varies widely for the product particles. Also, they are typically

readily dissolved, rendering them unsuitable for use as a sustained-release material. Further, there is no isolation of the pharmaceutical molecules from the environment or one another, leaving them susceptible to degradation by various mechanisms. Studies have shown that lyophilization of excipients can typically damage proteins rather than protect them. See, e.g., J. F. Carpenter, J. H. Crowe, "Infrared spectroscopic studies of the interaction of carbohydrates with dried proteins", Biochemistry 1989, 28, 3916-3922; J. F. Carpenter, S. Prestrelski, T. Arakawa, "Separation of freezing- and drying-induced denaturation of lyophilized proteins by stress-specific stabilization: I. Enzyme activity and calorimetric studies," Arch. Biochem. Biophys. 1993, 303, 456-464. K. Izutsu, S. Yoshioka, Y. Takeda, "The effects of additives on the stability of freeze-dried β-galactosidase stored at elevated temperatures", Int. J. Pharm. 1991, 71, 137-146. K. Izutsu, S. Yoshioka, T. Teroa, "Decreased protein-stabilizing effects of cryoprotectants due to crystallization", Pharm. Res. 1993, 10, 1232-1237.

Crystallized pharmaceuticals have been used in some instances, but there have been inherent limitations. Some API's , e.g. insulin, can be crystallized themselves, and are useful in that form for administration to patients. However, the majority of biopharmaceuticals either do not crystallize or the crystallization is very difficult, particularly on a commercial scale. Further, crystallization procedures are limited to the use of pharmaceutically-acceptable ingredients and process conditions that do not adversely affect the active pharmaceutical ingredient, thus further constraining the ability to obtain desired microcrystalline suspensions.

The fact that macromolecules are routinely isolated in sub-millimolar concentrations in a variety of crystals is known. See, e.g., K. Strupat, M. Karas, F. Hillenkamp, Int. J. Mass Spec. Ion Proc., 111, 89-102, 1991. Also, certain aromatic acids have been employed as hosts for biopolymer guests in crystals for use in matrix-assisted laser desorption ionization (MALDI) mass spectrometry, but not for the purposes of the present invention. See, Review by F. Hillenkamp, M. Karas, R.C. Beavis, B.T. Chait, Anal. Chem, 63, 1193A-1203A; S. Borman, Chem. Eng. News, 23-25, June 19, 1995. However, crystallization conditions in

these studies were optimized for characterization of the incorporated biopolymers. There were no investigations into optimizations that would be relevant to pharmaceutical preparations or operations such as homogeneity of the concentration of the inclusions, process scale-up, process robustness, chemical and physical stability of the preparations, suspendability in biocompatible solutions, preservative requirements and compatibility, container/closure system compatibility, and pharmacokinetic profiles.

The difficulty in obtaining suitable single crystals of some biopolymers has encouraged structural chemists to partially orient such molecules with electric, magnetic, or flow fields, by dissolution in liquid crystals or stretched gels, and as monolayers. In a similar effort, the isolation of biopolymers in a single crystal matrix has recently been studied in an effort to use such crystals for structural analysis of the biopolymers. Such isolation technique is described in "Single Crystal Matrix Isolation of Biopolymers," J. Chmielewski, J.J. Lewis, S. Lovell, R. Zutshi, P. Savickas, C.A. Mitchell, J.A. Subramony, and B. Kahr, J. Am. Chem. Soc. 1997, 119, 10565-10566. However, this article simply demonstrates that certain biopolymers are oriented by the host lattice, and the article suggests the use of such crystals for analyzing spectral anisotropies in biological molecules which could not otherwise be crystallized. This article does not discuss or suggest the use of this technique for enhancement of stability or sustained release of pharmaceuticals, or their administration to patients. Further, the proteins studied were not of pharmaceutical interest, the crystal materials described in this article, namely phthalic acid, gentisic acid and sinapic acid, were not selected or evaluated for biocompatibility, and the crystal sizes were not optimized for particular routes of administration. Therefore, the produced crystals with included biopolymers would not be suitable for administration to patients.

Other prior art procedures have required the use of polymers that are difficult to prepare, require harsh preparation conditions that can be harmful to the API's, and yield inconsistent results. For example, United States Patent No. 5,075,291 describes a process for preparing a uniformly-dispersed, pharmaceutically-active material in a crystalline sugar alcohol matrix. However,

this process requires the addition of the API into a molten sugar alcohol with considerable mechanical agitation. Many API's and virtually all biopharmaceuticals would not be stable in the extreme temperature of 110°C and the physical stresses of a high-shear vortex mixer used for agitation. The present invention does not require these extremes of temperature and physical agitation. Also, the process of the present invention slowly includes the API into the growing crystal lattice in specific growth sectors, instead of homogeneous mixing and entrapping of the active pharmaceutical ingredient in a viscous melt.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to pharmaceutical compositions comprising single crystals of a pharmaceutically-acceptable crystal lattice component, and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation. The crystals are prepared using components and methods which yield crystals having suitable purity and efficacy for use in administering the API's to a patient. The crystals may be coated or combined with adjuvants such as excipients, diluents or carriers, and are preferably formulated into tablets, capsules, suspensions, and other conventional forms containing dosage amounts of the API's. Alternatively, the crystals are prepared as depot formulations which may be administered, as by subcutaneous injection or implantation, to provide a long-term payout or sustained release of the active pharmaceutical ingredient. The present invention further provides methods for preparing the crystals and for storing and administering the active pharmaceutical ingredient either in crystal form or upon reconstitution to a solution.

Accordingly, it is an object of the present invention to provide single crystals which include API's in a growth-sector specific orientation. It is a feature of the invention that the API's are included at predictable, uniform concentrations that permit use of the crystals in formulating dosage amounts of the API's.

Another object of the present invention is to provide compositions comprising API's included in single crystals to provide improved stability and shelf-life. The active pharmaceutical ingredients may therefore be stored for extended periods of time prior to use either as crystals or as reconstituted solutions.

It is a further object of the present invention to provide single crystals with included API's to provide quick, delayed-release or sustained-release formulations for flexibility in pharmacokinetic profiles in delivery of the API's to patients.

Another object of the present invention is to provide pharmaceutical delivery units including an amount of single crystals sufficient to provide a dosage amount of the included active pharmaceutical ingredient. Alternatively, the pharmaceutical delivery units include a quantity of crystals sufficient to provide a

prolonged payout of the active pharmaceutical ingredient. The crystals may be coated or uncoated, and may be combined with various pharmaceutical adjuvants including excipients, diluents and carriers.

A further object of the present invention is to provide methods for preparing compositions comprising single crystals with growth-sector specific inclusions of API's.

It is another object of the present invention to provide methods for the storage and administration of API's utilizing inclusion of the API's within single crystals.

Other objects, features, and advantages of the present invention will be apparent to those skilled in the art from the following description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a photomicrograph illustrating fluorescence of a single crystal of green fluorescent protein in α-lactose monohydrate (1.8 (h) x 0.8 (w) x 0.5 (d) mm^3) with an idealized representation of habit. The sides of the crystal in the photomicrograph are bright due to internal reflection.

Figure 2 is a graph of the fluorescence decay of the green fluorescent protein at 333°K in several environments: mixed crystal in α-lactose monohydrate (triangle), saturated lactose solution (square), and lyophilized α-lactose monohydrate (diamond).

DESCRIPTION OF THE PREFERRED EMBODIMENT

For the purposes of promoting an understanding of the present invention, reference will now be made to the embodiments described hereafter. It will nevertheless be understood that no limitation of the scope of the invention is thereby intended, such modifications and applications of the principles of the invention as described herein being contemplated as would normally occur to one skilled in the art to which the invention relates.

The present invention utilizes single-crystal matrix inclusion of active pharmaceutical ingredients ("API's") to achieve advantageous storage and delivery of the API's. This invention has application to a wide range of API's to provide enhanced stability and/or delivery of the active pharmaceutical ingredients. For some applications, such as for many biopharmaceuticals, the invention is particularly advantageous in providing greater stability over time and in providing alternative delivery and sustained release formulations to patients .

The small molecule host crystals comprise a crystal lattice component which includes the API's in an oriented, growth-sector specific manner. The crystals and included API's are prepared to be pharmaceutically acceptable and pure, thereby being useful for administration to patients to be treated with the API's. As used herein, the term "pharmaceutically-acceptable" refers to sufficient quality to meet regulatory and compendial requirements for administration to humans and/or animals. The crystals provide a regular, predictable inclusion of the guest active pharmaceutical ingredient, and the crystals can consequently be used for obtaining a predetermined amount of the active pharmaceutical ingredient for delivery to a patient. In one aspect, the host crystal gradually dissolves upon contact with body tissue or fluids, and is therefore useful as a system for delivery of the active pharmaceutical ingredient into the body. Alternatively, the crystals and included active pharmaceutical ingredient may be reconstituted into a solution for administration to a patient.

The active pharmaceutical ingredient molecules are generally isolated from one another and are insulated from the environment by the host crystal. This leads to reduced susceptibility of the API to degradation, and therefore enhanced

stability and shelf-life. Also, the use of appropriate host crystal compounds, or selected dosage forms, permits the design of quick, delayed, or sustained-release formulations for delivery of the active pharmaceutical ingredient. Sustained-release formulations are particularly advantageous for treatment of chronic conditions as they provide a consistent amount of drug delivery over a long period of time to improve ease of use and patient compliance in administering the API.

The crystals preferentially incorporate the active pharmaceutical ingredient on certain faces, thereby providing a growth-sector specific inclusion and orientation to the API's. As used herein, the term "growth-sector specific inclusion and orientation," and equivalent terminology, refers to the fact that the API molecules are included primarily at certain faces of the crystal matrix. The growth-sector specific inclusion and orientation can be determined by one skilled in the art, as demonstrated in the examples herein, by fluorescence microscopy and anisotropy measurements, single crystal desorption mass spectrometry, and autoradiography of ^{14}C-labeled material. In one embodiment, at least about 0.001% (on weight/weight (w/w) basis) of the pharmaceutical is included within specific faces of the crystal matrix, and in another embodiment at least about 0.1% (w/w) and up to about 10%. The crystal parameters, including the particular crystal lattice component for a given API, the concentration of API, the use of crystal adjuvants, and the crystallization conditions, are selected to achieve the growth-sector specific inclusion and orientation of the API within the crystals.

The method of the present invention broadly involves the including of the active pharmaceutical ingredient into the single crystal matrix formed from a pharmaceutically-acceptable crystal lattice component. As used herein, the term "included" in the crystals refers to the active pharmaceutical ingredient being chemically adsorbed within the crystal lattice as the crystal is formed. This inclusion of the active pharmaceutical ingredient molecules is distinguished from crystallization of the API molecules with one another, and from simple and random entrapment of the API molecules by the formed crystal. The crystal product of the present invention is ordered, in contrast to the amorphous material produced by other approaches. The API is incorporated in the crystal in relation to its degree of

affinity for the crystal lattice molecules. The crystal lattice component is therefore selected to be both chemically and physically compatible with the API such that the API is received by the crystal during formation, and remains stable and efficacious while within the crystal and upon release therefrom.

In a typical approach, the including of the active pharmaceutical ingredient involves combining the crystal lattice component, the active pharmaceutical ingredient and a pharmaceutically-acceptable adjuvant in a liquid state. The crystal lattice component is then crystallized under pharmaceutically-acceptable conditions to form the inventive crystals. For example, one method uses spiking of the API into a saturated or supersaturated solution of the crystal lattice component in a suitable organic and/or aqueous solvent system. Alternately, the saturated or supersaturated solution of the crystal lattice component may be spiked into the API solution. Other components may also be added to the solution, including compounds which facilitate or modify crystal growth or which are desired for incorporation in the final formulation. The solution may be seeded using any of a variety of conventional techniques.

In one approach, the solution is allowed to evaporate and/or equilibrate to cooler conditions for growth of the crystals. The crystals are then grown as the solvent is slowly evaporated away and/or the solution is cooled, with the evaporation and temperature gradient conditions being selected dependent on such factors as the solvent system and the desired crystal size. The crystals containing the active pharmaceutical ingredient are harvested from the remaining solution and are preferably washed to remove surface contamination. This procedure yields crystals which include the active pharmaceutical ingredient at a predictable concentration and facial orientation.

In accordance with the present invention, crystals are grown under pharmaceutically-acceptable conditions. As used herein, the term "pharmaceutically-acceptable conditions" refers to the use of crystal and API compounds which are pharmaceutically-pure, and for which such pharmaceutical purity is maintained in the final crystals. The crystal and API compounds are pharmaceutically pure, or have pharmaceutical purity, if they are of sufficient

purity to be suitable for administration under applicable FDA or other administrative regulations regarding purity. The term pharmaceutically-acceptable conditions further refers to the use of crystallization conditions through which the API compounds retain pharmaceutical efficacy in the final crystals and upon subsequent administration to patients.

The present invention readily allows the inclusion of API's by affinity with the small host molecules in the growing crystal lattice. This overcomes many of the limitations associated with previous approaches. The processing involved with preparing the present crystals does not expose the API's to harsh conditions, thereby substantially reducing or avoiding the possible degradation or disruption of the structural aspects of the API which could occur with prior art techniques. The inventive crystals have an added advantage in that they do not interfere with normal analytical methodologies used for characterizing the pharmaceutical product. The small host molecules can be easily separated on the basis of molecular size, which is not the case for prior art techniques which use polymers that interfere with analytical methodologies.

The API molecules are incorporated into the host crystals typically at rates of at least about 0.001% (w/w), preferably at least about 0.1%, and more preferably about 1% to about 10% (w/w). Alternatively, the API molecules are included at rates of at least about 0.01%, and as much as at least about 1% (w/w). The limited molar concentration of the active pharmaceutical ingredient in the host crystals means that the active pharmaceutical ingredient molecules are generally isolated from one another in the crystals. Isolation of the API molecules is particularly advantageous for those molecules, such as certain biopharmaceuticals, which could otherwise react with one another (e.g., by polymerization) or the surrounding environment. The degree of isolation can be verified by those skilled in the art using atomic force microscopy or reaction fluorescence energy techniques. The present invention has a particular application to guest-host systems in which the guest API molecules are reactive with one another, but in which these molecules are sufficiently isolated from one another in the crystals as to substantially prevent such interaction. Consequently, the invention provides containment of the API

molecules in the solid state crystals and provides for the API to be comformationally stable.

The method preferably involves preparing a mixture of crystals of substantially uniform size. This may include processing of the harvested crystals, such as by grinding or milling, to reduce the crystals to a substantially uniform size. Greater uniformity can be achieved by sorting the processed crystals, such as by sieving. A preferred method further includes obtaining crystals which have a substantially uniform concentration of pharmaceuticals, for example, about 1% (w/w) of pharmaceuticals, that do not vary between crystals by more than 10 percent.

The method of the present invention may further include formulating the crystals into pharmaceutical preparations. For example, the collected crystals may optionally be coated with a suitable composition. Coated or uncoated crystals may be blended with one or more pharmaceutically-acceptable adjuvants, such as excipients, diluents, carriers or mixtures thereof. The blended crystals and adjuvant(s) are then formulated into pharmaceutical delivery units. In one embodiment, each unit includes a predetermined amount of the pharmaceutical. Alternatively, the crystals are combined in a delivery unit intended to deliver multiple or sustained dosing of the API over a period of time, such as by subcutaneous implantation of the delivery unit. A further aspect of the method of the present invention involves reconstituting the crystals to liquid form. In accordance with this method, the harvested crystals are dissolved in a suitable diluent for the crystal lattice component. The dissolution of the crystals releases the API from the crystals. The resulting solution may include other adjuvants, such as excipients, diluents or carriers, and the mixture is formulated under conventional procedures to desired delivery forms. In a particular aspect of the present invention, the crystals are used to store the pharmaceutical for a period of time, such as at least one month, or at least one year, and the crystals are subsequently dissolved to use the active pharmaceutical ingredient.

The present invention involves the use of any of a wide variety of pharmaceutically-acceptable host crystal systems that can incorporate API's in a

growing crystal lattice. The crystal lattice component is selected to be compatible with the guest API, and to be suited to the use of the resulting formulation for storage and administration. Selection of the crystal lattice component will involve consideration of such factors as affinity for the API, crystal size distribution and morphology, and desired pharmaceutical concentration and delivery rate, as well as other factors well known in the art of pharmaceutical delivery systems. The crystal systems must consistently incorporate the guest active pharmaceutical ingredient in terms of concentration and placement within the crystal lattice. The crystals also must grow under conditions which will not degrade or otherwise adversely affect the viability of the active pharmaceutical ingredient.

Preferred host crystal materials are those that have a high affinity for the included API. It appears that the oriented inclusion of the API's is related to the affinity between the crystal lattice component and the API. The affinity between these materials is therefore important in obtaining the desired inclusion of the API's, and also permits control of the inclusion based upon this affinity. For example, the concentration of the pharmaceutical in a crystal can be controlled by selecting the host component to have an affinity for the API which yields the desired inclusion rate. Also, mixtures of host materials, or of host materials and other excipients, can be used to provide an affinity yielding the desired inclusion level. In one aspect of the present invention, the API's are incorporated at levels of at least about 0.001% (w/w of guest:host), more preferably at least about 0.1% (w/w).

The preferred host crystal materials will also be very stable and readily crystallizable, and will maintain their "order" or crystal morphology when including a guest molecule, particularly large biomolecules. The use of particular host crystal components will also depend on such factors as how small or large the crystals can be produced and how readily they dissolve. For various routes of administration, it is desirable to have very small crystals (e.g., pulmonary), moderately sized crystals (e.g., injectable), or very large crystals (e.g., implantation and long term payout). The useful crystal sizes will therefore vary accordingly,

ranging from submicron to millimeter sizes. In one aspect of the present invention, the preferred crystals are in the order of 5-100 microns in size.

The useful host crystal systems are therefore diverse, and include various small molecule crystal systems which meet the desired criteria. Examples of pharmaceutically-acceptable crystal lattice components include sugars, polyhydroxy alcohols, single and polyamino acids, vitamins, salts, metals, preservatives, aromatic compounds especially aromatic acids, purified natural products, and polymers. Preferred crystal lattice components include, for example, sucrose, lactose, trehalose, maltose, galactose, sorbose, mannitol, lactitol, sorbitol, glycine, alanine, lysine, arginine, ascorbic acid, nicotinamide, thiamine, adenine, pyridoxine hydrochloride, caffeic acid, vanillic acid, ferulic acid, benzoate, sorbate, methyl paraben, sodium ascorbate, sodium saccharin, and potassium citrate. Also, compatible mixtures of these materials are also useful, and can be selected to obtain the desired rate of inclusion of the pharmaceutical, or to achieve desired characteristics, such as dissolution rate and pharmacokinetic profile, for the product crystals.

The crystal lattice components are selected to achieve the desired pharmacokinetics for the final crystals. As pertains to the present invention, the term "pharmacokinetics" is used to refer to the profile of the delivery of active pharmaceutical ingredient from the crystals into the circulatory system. This will depend primarily on the concentration of the active pharmaceutical ingredient in the crystals, as well as parameters of the active pharmaceutical ingredient itself. While given crystal lattice components will have associated inclusion and dissolution characteristics, these can be modified by including other crystal lattice components, other API's, or a variety of excipients. Thus, single crystals having two different, co-crystallized lattice components will typically be characterized by pharmacokinetic profiles different from crystals prepared with either of the crystal lattice components alone. Similarly, including excipients or other API's will provide altered rates of inclusion or dissolution for the resulting crystals, providing an associated modification in the pharmacokinetic profile for the resulting crystals.

In a related aspect, the present invention involves the use of mixtures of crystals having different pharmacokinetics in order to achieve desired payout profiles. For example, a pharmaceutical product can be obtained by combining two different types of crystals, one type of crystal using a first crystal lattice component characterized by a first pharmacokinetic profile, and the second type of crystal using a second crystal lattice component characterized by a second pharmacokinetic profile. The mixture of crystals will give a payout of API that is different from either of the individual payouts for the two crystal types.

The included API's are similarly diverse, limited simply by the requirements of compatibility with the host crystal and the crystal growth conditions. The active pharmaceutical ingredient cannot be unacceptably degraded or otherwise adversely affected by the conditions under which the crystals are formed. Also, the active pharmaceutical ingredient should remain stable for an extended period of time while included within the host crystal, and pharmaceutically efficacious upon release from the crystal.

Given the foregoing criteria, examples of API's useful in accordance with the present include: antibiotics (such as dirithryomycin, loracarbef, tilmicosin, vancomycin, tylosin, monensin), fluoxetine, raloxifene, olanzapine, and nizatidine. A more complete list of API's useful in accordancw with the present invention would include those identified in the following Table A.

TABLE A

Marketed Recombinant Protein Products

Tissue Plasminogen Activator, T-PA

- **Product name:** Activase (Generic name: Altepase)
- **Produced by:** Genentech
- **Indication:** Human use, Acute myocardial infarction
- **Date of approval:** Nov. 87, Patent expires on Dec. 2000.
- **Formulation:** Intravenous injection. Lyophilized powder which is reconstituted with sterile water (supplied) to 1mg/mL and results in a final pH of 7.3. Can not be reconstituted with preserved water due to precipitation. The 1mg/mL solution can be diluted 1:1 with 0.9% NaCl or D5W and help for 8 hours at room temperature. TPA is incapable with preservatives.

Ingredients	100 mg vial	50 mg vial	20 mg vial
T-PA	100 mg	50 mg	20 mg
L-Arginine	3.5 g	1.7 g	0.7 g
Phosphoric acid	1 g	0.5 g	0.2 g
Polysorbate 80	< 11 mg	< 4 mg	< 1.6 mg
Vacuum	No	Yes	Yes

- **Expression System:** Mammalian cell line (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 527 amino acids, sequence from human melanoma cell line, activity of 580,000 IU/mg.
- **Additional Information:** Sales > $100 million. Cost of therapy $2,750 (100 mg).

Interferon Gamma-1b

- **Product name:** Actimmune
- **Produced by:** Genentech
- **Indication:** Human use, chronic granulomatous disease
- **Date of approval:** Dec. 1990
- **Formulation:** Single dose solution formulation (0.5 mL), subcutaneous injection. Each 0.5 mL contains 100 µg interferon gamma-1b, 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg polysorbate-20 in sterile water.
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Post-Transitional Modification:**
- **Structure:** Single chain; Human sequence, 140 amino acids, 16,465 molecular weight, non-covalent dimeric form in solution, activity of 30 Million units/mg.
- **Additional Information:** 14% injection site irritation vs. 2% in placebo. Cost $140 for 50µg.

Interferon alfa-n3 (natural source, not recombinant)

- **Product name:** Alferon N
- **Produced by:** Interferon Science (New Brunswick, NJ)

- **Indication:** Human use, Genital Warts
- **Date of approval:** Jun 90
- **Formulation:** Preserved solution formulation (each mL contains 5 million IU of interferon alfa-n3 in phosphate buffered saline containing 3.3 mg phenol and 1 mg human albumin). Injected intralesional twice weekly for up to 8 weeks (50μL injected into each wart, 500μL total dose per treatment).
- **Expression System:** Natural source – human leukocytes which are exposed to an avian virus in order to produce interferon.
- **Refolding Conditions:** None
- **Structure:** Approximately 166 amino acids with a molecular weight ranging from 16 to 27 kDa, specific activity of 20,000 IU/mg or greater.
- **Additional Information:** Cost $142 per mL.

Beta Interferon Ia

- **Product Name:** Avonex
- **Produced by:** Biogen (Cambridge, MA)
- **Indication:** Human use, Multiple Sclerosis
- **Date of approval:** May 95
- **Formulation:** Lyophilized powder (stored refrigerated or at 25 °C for <30 days) which is reconstituted with sterile water (supplied, 1.1 mL) to 30 μg/mL beta interferon 1a, 15 mg/mL human albumin, 5.8 mg/ml NaCl, 5.7 mg/ml dibasic Na phosphate, 1.2 mg/ml monobasic sodium phosphate, and has a pH of approximately 7.3 (recon solution is stable for 6 hours at refrigerated temperatures). Weekly intramuscular injection by patient or doctor (dosed for 1-2 years in clinical trials).
- **Expression System:** Mammalian cells (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein (single N-linked complex carbohydrate), 166 amino acids with a predicted molecular weight of 22,500 daltons, human sequence, has a specific activity of 200 million units per mg protein.
- **Additional Information:** Cost $180 per vial (33μg).

Interferon beta-1b

- **Product Name:** Betaseron
- **Produced by:** Berlex Laboratories (Wayne, NJ and Chiron, Emeryville, CA)
- **Indication:** Human use, Multiple Sclerosis
- **Date of approval:** July 93
- **Formulation:** Lyophilized product (stored refrigerated) which is reconstituted with 0.54% NaCl (supplied, to 0.25 mg/mL interferon beta-1b, 12.5 mg/mL human albumin, 12.5 mg/ml dextrose, and has a pH of approximately 7.3 (recon solution is stable for 3 hours). Injected subcutaneously every other day (chronic use).
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Structure:** 165 amino acids with an approximate molecular weight of 18,500 daltons, human sequence but with a serine or cysteine at residue 17.

Recombinant form does not contain the carbohydrate moiety found in the natural material. Has a specific activity of 32 million units per mg protein.

- **Additional Information:** Sales > $500 million. Cost of therapy is $13,140 (based on 0.25 mg/injection, dose every other day for 1 year; equals 46 mg protein).

Interferon alfa-2b

- **Product Name:** Intron A
- **Produced by:** Schering-Plough (Madison, NJ)
- **Indication:** Human use, Hairy cell leukemia, genital warts, Hepatitis, Melanoma, Kaposi's sarcoma
- **Date of approval:** June 86
- **Formulation:** Comes in a lyophilized and a solution formulation. The lyophilized formulations when reconstituted with 0.9% benzyl alcohol (supplied) contains either 0.015, 0.025, 0.05, 0.90, or 0.125 mg/mL. Interferon alfa-2b, 20 mg/ml glycine, 2.3 mg/ml sodium phosphate dibasic, 0.55 mg/ml sodium phosphate monobasic, 1 mg/ml human albumin, 1.2 mg/mL methylparaben, and 0.12 mg/ml propylparaben. These formulations be injected intramuscular, subcutaneous, or intralesional. All formulations and reconstituted products are stored at refrigerated temperatures.
- **Expression System:** *E. coli*
- **Refolding Conditions:**
- **Structure:** Water soluble protein a molecular weight of 19,271 daltons. The interferon alfa-2b gene is derived from human leukocytes.
- **Additional Information:** Sales > $500 Million. Cost of therapy is $16,445 (5 million units every day for 1 year, this is equal to 9 mg protein). Specific activity is 200 million units per mg protein.

Interferon alfa-2a

- **Product Name:** Roferon-A
- **Produced by:** Hoffmann-La Roche (Nutley, NJ)
- **Indication:** Human use, Hairy cell leukemia, genital warts, Hepatitis, Melanoma, Kaposi"sarcom, myelogenous leukemia
- **Date of approval:** June 1986
- **Formulation:** Multi-use and lyophilized formulation indented for intramuscular or subcutaneous administration. Multi-use formulation contains either 0.015, 0.045, 0.090, 0.18 mg/mL. Interferon alfa-2a, 9 mg/ml NaCl, 5 mg/ml human albumin, and 3 mg/ml phenol. The lyophilized formulation reconstituted with 3 mL of supplied diluent (6 mg/ml NaCl, 3.3 mg/ml phenol) consists of 0.03 mg/ml Interferon alfa-2a, 9mg/ml NaCl, 1.67 mg/ml human albumin, and 3.3 mg/ml phenol.
- **Expression System:** *E. coli* (tetracycline promoter).
- **Refolding Conditions:**
- **Structure:** Protein of 165 amino acids having a molecular weight of 19,000 daltons

- **Additional Information:** Cost of therapy is $59,200 (28mg protein over 1 year). Specific activity is 200 million international units per mg protein.

Human Growth Hormone (Somatropin)
- **Product Name:** Bio Tropin
- **Produced by:** Bio-Technology General (Iselin, NJ)
- **Indication:** Human use, Growth Deficiency
- **Date of approval:** May 95
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)
- **Product Name:** Genotropin
- **Produced by:** Pharmacia and Upjohn (Kalamazoo, MI)
- **Indication:** Human Use, Growth Deficiency
- **Date of approval:** Aug 95
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)
- **Product Name:** Humatrope
- **Produced by:** Eli Lilly (Indianapolis, IN)
- **Indication:** Human use, Growth Deficiency
- **Date of approval:** March 87
- **Formulation:** Lyophilized product which is reconstituted with sterile water containing 0.3% m-cresol, 1.7% glycerin (supplied) to 2 mg/mL hGH and has a final pH of approximately 7.5, subcutaneous or intramuscular administration. Each 5 mg lyophilized vial contains 5 mg hGH, 25 mg mannitol, 1.13 mg dibasic sodium phosphate, and 5 mg glycine.
- **Expression System:** *E. coli.*
- **Refolding Conditions:**
- **Structure:** 191 amino acids, molecular weight of 22,125 daltons, sequence is identical to human pituitary-derived material.
- **Additional Information:** Cost $210 per 5 mg hGH

Human Growth Hormone (Somatropin)
- **Product Name:** Norditropin
- **Produced by:** Novo Nordisk (Princeton, NJ)

- **Indication:** Human use, Growth Deficiency
- **Date of approval:** July 91
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:**

Human Growth Hormone (Somatropin)

- **Product Name:** Nutropin and Nutropin AQ
- **Produced by:** Genentech
- **Indication:** Human use, Growth Deficiency
- **Date of approval:** March 1994
- **Formulation:** Lyophilized product which is reconstituted with bacteriostatic water (0.9% benzyl alcohol, supplied) to 5 mg/mL hGH and has a final pH of approximately 7.4, subcutaneous or intramuscular administration. Each 5 mg lyophilized vial contains 5 mg hGH, 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg monobasic and 1.3 mg dibasic), and 1.7 mg glycine.
- **Expression System:** *E. coli*, expressed with a leading secretion signal precursor which directs the protein to the plasma membrane of the cell where the sequence is removed and the native protein is secreted into the periplasm so that the protein if folded appropriately as it is synthesized.
- **Refolding Conditions:** None, expressed folded in E. coli.
- **Structure:** 191 amino acids, molecular weight of 22,125 daltons, sequence is identical to human pituitary-derived material.
- **Additional Information:** Cost $420 per 10 mg hGH.

β-Glucocerebrosidase (imiglucerase)

(β-D-Glucosyl-N-acylsphingosine glucohydrolase, E.C.3.2.1.45)

- **Product Name:** Cerezyme
- **Produced by:** Genzyme (Cambridge, MA)
- **Indication:** Human use, Graucher's disease
- **Date of approval:** May 94
- **Formulation:** Lyophilized product (212 units glucocerebrosidase, 155 mg mannitol, 70 mg sodium citrate, and 0.53 mg polysorbate-80; stored refrigerated) is reconstituted with 5.1 mL of sterile water, final pH is approximately 6.1. The reconstituted material is combined with 100 to 200 mL of 0.9% NaCl and administered intravenously.
- **Expression System:** Mammalian cell culture (Chinese Hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites, molecular weight is 60,430 daltons. Recombinant protein differs from human placental glucocerebrosidase by a arginine substitued for histidine at position 495 and the glycosylation sites have been modified to terminate in mannose sugars (which are specifically recognized by endocytic

carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease).

- **Additional Information:** Orphan Drug, sales > $100 million, Cost of therapy is $351,130 (1 year).

Hepatitis B Surface Antigen

- **Product Name:** Engerix-B
- **Produced by:** SmithKline Beechman (Philadelphia, PA
- **Indication:** Human use, Hepatitis B
- **Date of approval:** Sept 89
- **Formulation:** Suspension (20μg/mL hepatitis B surface antigen adsorbed onto 0.5 mg aluminum, 1:20,000 thimerosal, 9 mg/ml NaCl, 1.7 mg/ml sodium phosphates). Intramuscular administration.
- **Expression System:** A portion of the hepatitis B virus gene, coding for hepatitis B surface antigen, in cloned into yeast (*Sacccharomyces cerevisiae)*
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:** Formulation contains no more that 5% yeast proteins.

Hepatitis B Surface Antigen

- **Product Name:** Recombivax HB
- **Produced by:** Merck (Whithouse Station, NJ)
- **Indication:** Human use, Hepatitis B prevention
- **Date of approval:** July 1986
- **Formulation:** Suspension (10μg/mL hepatitis B surface antigen adsorbed onto 0.5 mg aluminum, 1:20,000 thimerosal) Intramuscular administration.
- **Expression System:** A portion of the hepatitis B virus gene, coding for hepatitis B surface antigen, in cloned into yeast (*Sacccharomyces cerevisiae)*
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:** Formulation contains no more that 1% yeast proteins.

Erythropoietin (rEPO)

- **Product Name:** Epogen or Epoetin alfa (also sold under the name Procrit by Ortho Biotech but manufactured by Amgen)
- **Produced by:** Amgen (Thousand Oaks, CA)
- **Indication:** Human use, Anemia
- **Date of approval:** June 89, Patent expires in 2004 (December)
- **Formulation:** Two solution formulations, single dose and multi-dose. Single-dose is preservative free and each mL contains 2000, 3000, 4000, or 10000 units Epogen, 2.5 mg human albumin, 5.8 mg sodium citrate, 5.8 NaCl, and 0.06 mg citric acid in water for injection, pH 6.9 +/- 0.3. The preserved multi-dose product contains 10,000 units Epogen, 2.5 mg human albumin, 1.3 mg

sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid and 1% benzyl alcohol per mL of solution, pH is 6.1 +/- 0.3. Both solutions are stored refrigerated.

- **Expression System:** Mammalian cell
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 165 amino acids having a molecular weight of 30,400 daltons, sequence identical to that of the human protein.
- **Additional Information:** Sales > $500 million, Cost $120 for 10,000 units.

Human Insulin

- **Product Name:** Humulin
- **Produced by:** Eli Lilly (Indianapolis, IN)
- **Indication:** Human use, Diabetes
- **Date of approval:** Oct 82
- **Formulation:**
- **Expression System:** *E. Coli*
- **Refolding Conditions:**
- **Structure:**
- **Additional Information:** Sales > $500 Million

Human Insulin

- **Product Name:** Novolin
- **Produced by:** Novo Nordisk (Princeton, NJ)
- **Indication:** Human use, Diabetes
- **Date of approval:** July 91
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications**
- **Structure:**
- **Additional Information:**

LysPro Human Insulin

- **Product Name:** Humulog
- **Produced by:** Eli Lilly (Indianapolis, IN)
- **Indication:** Human use, Diabetes
- **Date of approval:** June 1996
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications**
- **Structure:**
- **Additional Information:**

GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor)

- **Product Name:** Leukine
- **Produced by:** Immunex (Seattle, WA)
- **Indication:** Human use, Bone marrow transplantation, Hodgkin's Disease, Leukemia
- **Date of approval:** Mar 91
- **Formulation:** Lyophilized solution which is reconstituted with sterile water (stored at refrigerated temperatures for <6 hours) or 0.9% benzyl alcohol (can be stored for <20 days at refrigerated temperatures) and administered intravenous. After reconstitution, the lyophilized single use product contains either 0.25 mg/mL or 0.50 mg/mL GM-CSF, 40 mg/Ml mannitol, 10 mg/ml sucrose, and 1.2 mg/ml tromethamine (final pH is 7.4 +/- 0.3). The reconstituted solution is then diluted into a 0.9% NaCl bag for IV administration (note if final GM-CSF is below 0.01 mg/mL add human albumin to 0.1% to prevent adsorption to the IV bag.
- **Expression System:** Yeast (*S. Cerevisiae)*
- **Refolding Conditions:** None, expressed folded
- **Structure:** Glycoprotein of 127 amino acids characterized by 3 primary molecular species having molecular masses of 19,500, 16800, and 15500 daltons. The primary sequence differs from natural human GM-CSF by a substitution of leucine at position 23, and the carbohydrate moiety may be different from native.
- **Additional Information:** Specific activity is $5X10^7$ colony forming units per mg protein. Sargramostim is the proper name for yeast-derived recombinant GM-CSF. Cost for a 0.5 mg GM-CSF vial is $178.

G-CSF (Granulocyte Colony Stimulating Factor)

- **Product Name:** Neupogen
- **Produced by:** Amgen (Thousand Oaks, CA)
- **Indication:** Human use, Neutropenia, bone marrow transplantation, anemia
- **Date of approval:** Feb 91
- **Formulation:** Single-use solution formulation containing 0.3 mg/mL G-CSF, 10 mM sodium acetate, 5% mannitol, and 0.004% Tween-80 at a pH of 4. The product is to be stored at refrigerated temperatures and no more than 24 hours at room temperature. If required, Neupogen can be diluted with D5W (do not dilute with saline at any time; product may precipitate), at concentrations below 5 to 15µg/mL, and human albumin to 2 mg/mL to prevent adsorption to IV bag.
- **Expression System:** *E. coli.*
- **Refolding Conditions:**
- **Structure:** A 175 amino acid protein with a molecular weight of 18,800 daltons. The protein has an amino acid sequence identical to the human protein except for an additional N-terminal methionine (necessary for expression in *E. coli*). The human protein is glycosylated but the recombinant Neupogen is not.
- **Additional Information:** Sales > $500 million. Filgrastim is the name given to recombinant methionyl human G-CSF. Cost of therapy (lung cancer) is $2,130

(4.2 mg protein over 14 days). Specific activity is 30 million units per mg protein.

Satumomab Pendetide

- **Product Name:** OncoScint CR/OV
- **Produced by:** Cytogen (Princeton, NJ)
- **Indication:** Human use, Colorectal and ovarian cancers
- **Date of approval:** Dec 92
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**

Additional Information:

Interleukin-2

- **Product Name:** Proleukin (generic name: Aldesieukin)
- **Produced by:** Chiron (Emeryville, CA)
- **Indication:** Human use, Renal cell carcinoma
- **Date of approval:** May 1992
- **Formulation:** Single-use lyophilized formulation which is reconstituted with 1.2 mL sterile water and administered intravenously. Each reconstituted product contains 1.1 mg/mL Proleukin, 50 mg/ml mannitol, and 0.18 mg/ml dibasic sodium phosphate (pH is 7.5 +/- 0.3). Lyophilized product is stored at refrigerated temperatures, reconstituted product is stable up to 48 hours at refrigerated to room temperatures, but should be stored in refrigerator due to lack of preservatives. Addition of preservatives results in increased aggregation, addition of human albumin alters pharmacology.
- **Expression System:** *E. Coli* (tetracycline promoter).
- **Refolding Conditions:**
- **Structure:** Proleukin has a molecular weight of 15,300 daltons and differs from the natural human protein (is not glycosylated, the N-terminal alanine is removed, and has a serine substituted for the free cysteine at position 125).
- **Additional Information:** Specific activity is 18 million international units per 1.1 mg protein. Cost is $395 per 1.3 mg protein.

Somatrem

- **Product Name:** Protropin
- **Produced by:** Genentech (S. San Francisco, CA)
- **Indication:** Human use, Growth deficiency
- **Date of approval:** Oct 1985, patent expired on Oct 1992
- **Formulation:** Lyophilized formulation which is reconstituted with 0.9% benzyl alcohol (supplied) and administered intramuscular or subcutaneous. The lyophilized vial contains 5 mg Somatrem, 40 mg mannitol and 1.7 mg sodium phosphates (0.1 mg sodium phosphate monobasic and 1.6 mg sodium phosphate dibasic) and is reconstituted with 1 to 5 mL of 0.9% benzyl alcohol.

The lyophilized product is stored at refrigerated temperatures, the reconstituted product is good for 14 days at refrigerated temperatures.

- **Expression System:** *E. Coli*
- **Refolding Conditions:**
- **Structure:** Contains 192 amino acids with a molecular weight of 22,000 daltons. Identical to human sequence but contains an extra methionine at the N-terminus.
- **Additional Information:** Sales > $100 million. Cost of therapy is $13,110 (1 year, 313 mg protein)

Dnase (deoxyribonuclease I)

- **Product Name:** Pulmozyme
- **Produced by:** Genentech (S. San Francisco, CA)
- **Indication:** Human use, Cystic fibrosis
- **Date of approval:** Dec 1993
- **Formulation:** Inhalation solution (aerosol mist produced by a compressed air driven nebulizer system). Comes in a single-use 2.5 mL ampule containing 1.0 mg/mL Dnase, 0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/ml sodium chloride, at a pH of 6.3. The solution is stored at refrigerated temperatures and should not be exposed to light.
- **Expression System:** Mammalian cells (Chinese hamster Ovary cells)
- **Refolding Conditions:**
- **Structure:** Glycoprotein of 260 amino acids having a molecular weight of 37,000 daltons. The primary sequence is identical to that of the native human enzyme.
- **Additional Information:** Sales > $100 Million. Cost is $32 for 2.5 mg of protein (1 ampule)

M-CSF (Macrophage-Colony Stimulating Factor)

- **Product Name:** Leucomax (generic name: Molgramostim)
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** FDA unapproved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Epoetin Beta (Erythropoietin)

- **Product Name:** Marogen
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:**

- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Polyribonucleotide

- **Product Name:** Ampligen
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** FDA Unapproved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Human Serum Albumin

- **Product Name:**
- **Produced by:**
- **Indication:**
- **Date of approval:**
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Septomonab?

- **Product Name:** Gentoxin
- **Produced by:**
- **Indication:** Human use,
- **Date of approval:** Not FDA approved
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

Protein

- **Product Name:**

- **Produced by:**
- **Indication:**
- **Date of approval:**
- **Formulation:**
- **Expression System:**
- **Refolding Conditions:**
- **Post-Transitional Modifications:**
- **Structure:**
- **Additional Information:**

TABLE A

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Coravax ™ Haemophilus b conjugate (meningococcal protein conjugate) and hepatitis b (recombinant) vaccine	Merck Whitehouse Station, NJ	recombinant vaccine	vaccination of infants beginning at two months of age against both invasive Haemophilus influenzae type b diseases (Hib) and hepatitis B (October 1996)
Engenix-B® Hepatitis B vaccine (recombinant)	SmithKline Beecham Philadelphia, PA	recombinant vaccine	hepatitis B (September 1989)
EPOGEN® Epoetin alfa (rEPO)	Amgen Thousand Oaks, CA	erythropoletin	treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir treated HIV-infected patients (June 1989); treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (April 1993); prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (December 1996)

PROCRIT® Epoetin alfa (rEPO)	Ortho Biotech Raritan, NJ	erythropoletin	treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis, and anemia in Retrovir treated HIV-infected patients (June 1989); treatment of anemia caused by chemotherapy in patients with non-myeloid malignancies (April 1993); prevention of anemia associated with surgical blood loss, autologous blood donation adjuvant (December 1996)

(PROCRIT was approved for marketing under Amgen's epoetin alfa PLA. Amgen manufactures the product for Ortho Biotech.) Under an agreement between the two companies, Amgen licensed to Ortho Pharmaceutical the U.S. rights to epoetin alfa for indications for human use excluding dialysis and diagnostics.

Genotropin™ somatropin (rDNA origin) for injection	Pharmacia & Upjohn Kalamazoo, MI	human growth hormone	short stature in children due to growth hormone deficiency (August 1995)
Geref® human growth hormone releasing factor	Serono Laboratories Norwell, MA	growth factor	evaluation of the ability of the somatotroph of the pituitary gland to secrete growth hormone (December 1990); pediatric growth hormone deficiency (October 1997)
Gonal-F® recombinant human follicle-stimulating hormone (r-FSH)	Serono Laboratories Norwell, MA	recombinant fertility hormone	female infertility (September 1997)
Humalog™ insulin lispro	Eli Lilly Indianapolis, IN	recombinant insulin	diabetes (June 1996)
Humatrope® somatropin (rDNA origin) for injection	Eli Lilly Indianapolis, IN	humane growth hormone	human growth hormone deficiency in children (March 1987)

TABLE A

5

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Humulin® human insulin (recombinant DNA origin)	Eli Lilly Indianapolis, IN	recombinant insulin	diabetes (October 1982)
Infergen® interferon alfacon-1	Amgen Thousan Oaks, CA	interferon	treatment of chronic hepatitis C viral infection (October

			1997)
Intron® A interferon alfa-2b (recombinant)	Schering-Plough Madison, NJ	interferon	hairy cell leukemia (June 1986); genital warts (June 1988); AIDS-related Kaposi's sarcoma (November 1988); hepatitis C (February 1991); hepatitis B (July 1992); malignant melanoma (December 1995); follicular lymphoma in conjunction with chemotherapy (November 1997)
KoGENate® antihemophiliac factor (recombinant)	Bayer Corporation, Pharmaceutical Division West Haven, CT	clotting factor	treatment of hemophilia A (February 1993)
Leukine™ sargramostim (GM-CSF)	Immunex Seattle, WA	colony stimulating factor	autologous bone marrow transplantation (March 1991); neutropenia resulting from chemotherapy in acute myelogenous leukemia (September 1995); allogeneic bone marrow transplantation (November 1995); peripheral blood progenitor cell mobilization and transplantation (December 1995)
MyoScint® imiclromab penietate	Centocor Malvern, PA	MAb	myocardial infarction imaging agent (July 1996)
Neumega® oprelvekin	Genetics Institute Cambridge, MA	MAb	prevention of severe chemotherapy-induced thrombocytopenia (November 1997)
NEUPOGEN® Filgrastim (rG-CSF)	Amgen Thousand Oaks, CA	colony stimulating factor	chemotherapy-induced neutropenia (February 1991); autologous or allogeneic bone marrow transplantation (June 1994); chronic severe neutropenia (December 1994); support peripheral blood progenitor cell transplantation (December 1995)
Norditropin® somatropin (rDNA orgin) for injection	Novo Nordisk Pharmaceuticals Princeton, NJ	human growth hormone	treatment of growth failure in children due to inadequate growth hormone secretion (May 1995)
Novolin® 70/30 70% NPH human insulin isophane suspension & 30% regular, human insulin injection (recombinant DNA origin)	Novo Nordisk Pharmaceuticals Princeton, NJ	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)

Novolin® L Lente®, human insulin zinc suspension (recombinant DNA origin)	Novo Nordisk Pharmaceuticals Princeton, NJ	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Novolin® N NPH human insulin isophane suspension (recombinant DNA origin)	Novo Nordisk Pharmaceuticals Princeton, NJ	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)
Novolin® R regular, human insulin (recombinant DNA origin)	Novo Nordisk Pharmaceuticals Princeton, NJ	recombinant insulin	insulin-dependent diabetes mellitus (July 1991)
Nutropin® somatropin for injection	Genentech S. San Francisco, CA	human growth hormone	growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (March 1994); Turner's syndrome (December 1996); growth hormone inadequacy in adults (December 1997)
Nutropin AQ™ somatropin (liquid)	Genentech S. San Francisco, CA	human growth hormone	growth failure in children due to chronic renal insufficiency, growth hormone inadequacy in children (December 1995); Turner's syndrome (December 1996); growth hormone inadequacy in adults (December 1997)
OncoScint® CR/OV satumomab pendetide	CYTOGEN Princeton, NJ	MAb	detection, staging and follow-up of colorectal and ovarian cancers (December 1992)
ORTHOCLONE OKT® 3 muromonab-CD3	Ortho Biotech Raritan, NJ	MAb	reversal of acute kidney transplant rejection (June 1986); reversal of heart and liver transplant rejection (June 1993)
Proleukin® aldesleukin (interleukin-2)	Chiron Emeryville, CA	interleukin	renal cell carcinoma (May 1992); metastatic melanoma (January 1998)
ProstaScint® capromab pentetate	CYTOGEN Princeton, NJ	MAb	detection, staging and follow-up of prostate adenocarcinoma (October 1996)

Protropin® somatrem for injection	Genentech S. San Francisco, CA	human growth hormone	human growth hormone deficiency in children (October 1985)
Pulenozyme® domase alpha, recombinant	Genentech S. San Francisco, CA	recombinant DNase	cystic fibrosis (December 1993); management of advanced cystic fibrosis (December 1996)
Recombinate™ antihemophilic factor recombinant (rAHF)	Baxter Healthcare/Hyland Division Glendale, CA Genetics Institute Cambridge, MA	clotting factor	hemophilia A (December 1992)
RECOMBIVAX HB® hepatitis B vaccine (recombinant), MSD	Merck Whitehouse Station, NJ	recombinant vaccine	hepatitis B prevention (July 1986)
Refludan™ lepirudin (rDNA) for injection	Hoechst Marion Roussel Kansas City, MO	recombinant anticoagulant	heparin-induced thrombocysopenia type II (March 1998)

APPROVED BIOTECHNOLOGY DRUGS AND VACCINES

Product Name	Company	Product Category	Indication
Regranex® becaplermin	Ortho-McNeil Pharmaceuticals Raritan, NJ	growth factor	lower extremity diabetic neuropathic ulcers (December 1997)
ReoPro® abciximab	Censocor Malvern, PA Eli Lilly Indianapolis, IN	MAb	anti-platelet prevention of blood clots in the setting of high-risk percutaneous transluminal coronary angioplasty (December 1994); refractory unstable angina when percutaneous coronary intervention is planned (November 1997)
Retevase™ reteplase	Boehringer Mannheim Gaithersburg, MD Centocor . Malvern, PA	tissue plasminogen factor	treatment of acute myocardial infarction (October 1996)
Rituxan® rituximab	Genentech S. San Francisco, CA IDEC Pharmaceuticals San Diego, CA	MAb	treatment of relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma (November 1997);
Roferon®-A interferon alfa-2a, recombinant	Hoffmann-La Roche Nutley, NJ	interferon	hairy cell leukemia (June 1986); AIDS-related Kaposi's sarcoma (November 1988); chronic myelogenous leukemia (November 1995); hepatitis C (November 1996)

Saizen® somatropin (rDNA origin) for injection	Serono Laboratories Norwell, MA	human growth hormone	pediatric growth hormone deficiency (October 1996)
Serostim ™ somatropin (Rdna origin) for injection	Serono Laboratories Norwell, MA	human growth hormone	treatment of AIDS-associated catabolism/wasting (August 1996); pediatric HIV failure to thrive (February 1998)
Verluma® nofetumornab	Boehringer Ingelheim Ridgefield, CT NeoRx Seattle, WA	MAb	detection of small-cell lung cancer (August 1996)
Vistide® cidosovir injection	Gilead Sciences Foster City, CA	nucleotide analogue	cytomegalovirus retinitis in AIDS patients (June 1996)
Zenapaz® daclizumab	Hoffmann-La Roche Nutley, NJ	MAb	prevention of acute kidney transplant rejection (December 1997)

The content of this survey has been obtained through government and industry sources based on the latest information. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly.

PhRMA Internet address: http://www.phrma.org

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BIOTECHNOLOGY MEDICINES IN DEVELOPMENT

AIDS/HIV INFECTION AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
AD-439 and AD-519 combination	Tanox Biosystems Houston, TX	MAb	HIV infection, AIDS	Phase II
AD-439 MAb, anti-HIV to V3 loop of gp 120 protein; neutralizing antibody	Tanox Biosystems Houston, TX	MAb	HIV infection, AIDS	Phase II
AD-519 MAb, anti-HIV to C4 region of gp 120 protein; neutralizing antibody	Tanox Biosystems Houston, TX	MAb	HIV infection, AIDS	Phase II
Alferon LDO® interferon alfa-n3	Interferon Sciences New Brunswick, NJ	interferon	AIDS-related complex, AIDS	Phase I/II
Alferon N injection® interferon alfa-n3	Interferon Sciences New Brunswick, NJ	interferon	HIV infection (see also infectious diseases)	Phase III
			co-infection (HIV/HCV)	Phase II

ALVAC-MN 12-TMG (vCP205)	Pasteur Merieux Connaught Lyons, France Virogenetics Albany, NY	vaccine	HIV infection	Phase II
Ampligen®	Hemispherx Biophama New York, NY	interferon	HIV infection (see also cancer, infectious diseases, other)	Phase II
autologous gene-modified hematopoietic stem cells	SyStemix Palo Alto, CA	gene therapy	HIV infection	Phase I
gene therapy	Cell Genesys Foster City, CA Hoechst Marion Roussel Kansas City, MO	gene therapy	HIV infection	Phase II
gp 120 vaccine	VaxGen S. San Francisco, CA	vaccine	AIDS	Phase II
HIV-IT(V) Retrovector ™ HIV-1 111B env/rev retroviral vector	Chiron Viagene San Diego, CA	gene therapy	asymptomatic HIV-1 infection	Phase II
HIV Vaccine (gp 120)	Chiron Emeryville, CA	vaccine	AIDS	Phase II
interleukin-10 (IL-10)	Schering-Plough Madison, NJ	interleukin	HIV disease (see also autoimmune, digestive heart, neurologic, respiratory, skin)	Phase I

AIDS/HIV INFECTION AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
ISIS 2922 fomivirsen	Isis Pharmaceuticals Carlsbad, CA	antisense	cytomegalovirus retinitis	Phase III
ISIS 13312	Isis Pharmaceuticals Carlsbad, CA	antisense	cytomegalovirus retinitis	Phase I
Leukine™ sargramostim (GM-CSF)	Immunex Seattle, WA	colony stimulating factor	adjuvant to AIDS therapy, HIV infection, prevention of infection in HIV patients (see also cancer.)	Phase II

memantine	Neurobiological Technologies Richmond, CA		AIDS dementia complex and AIDS-related neuropathic pain (see also diabetes)	Phase II
MPL® immunomodulator vaccine	Ribi ImmunoChem Hamilton, MT	vaccine	AIDS (see also infectious diseases)	Phase I
NEUPOGEN® Filgrastim (rG-CSF)	Amgen Thousand Oaks, CA	colony stimulating factor	treatment and prevention of neutropenia in HIV patients (see also cancer, respiratory)	application submitted
Ovidrel® recombinant human chorionic gonadotropin (r-hCG)	Ares-Serono and Serono Laboratories Norwell, MA	recombinant gonadotropin	Kaposi's sarcoma, AIDS-related hypogonadism (see also infertility)	Phase I/II
PEG interleukin-2	Chiron Emeryville, CA	interleukin	HIV infection in combination with Retrovir®	Phase II
PMPA	Gilead Sciences Foster City, CA	nucleotide analogue	HIV infection, AIDS	Phase II
Prevention ™ adefovir dipivoxil	Gilead Sciences Foster City, CA	nucleotide analogue	HIV infection, AIDS	Phase III
PRO 367	Progenics Pharmaceuticals Tarrytown, NY		HIV infection	Phase I
PRO 542	Progenics Pharmaceuticals Tarrytown, NY		HIV infection	Phase I
Proleukin® aldesleukin (interleukin-2)	Chiron Eneryville, CA	interleukin	HIV infection in combination with Retrovir® (see also cancer)	Phase II/III
Rensune HIV-1 immunogen	Immune Response Corp. Carlsbad, CA	immune-based therapy	HIV seropositive	Phase III
retroviral vector with 2 ribozymes	Chiron Emeryville, CA	gene therapy	HIV infection	Phase I/II
TBC-3B (vaccinia virus expressing HIV genes env, gag and pal)	Therion Biologics Cambridge, MA	vaccine	AIDS prevention	Phase I

AUTOIMMUNE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
adenosine deaminase-transduced autologous CD34+PBC or umbilical cord/placental blood cells	National Cancer Institute Bethesda, MD	gene therapy	severe combined immunodeficiency	Phase I NCI Trial
adenosine deaminase-transduced T cells	National Cancer Institute Bethesda, MD	gene therapy	severe combined immunodeficiency	Phase I NCI Trial
AnergiX ™-RA	Anergen Redwood City, CA	functional antigenics immuno-therapy	rheumatoid arthritis	Phase I
AnervaX™	Anergen Redwood City, CA	peptide vaccine	rheumatoid arthritis	Phase II
Avakine ™ chimeric anti-TNF antibody	Centocor Malvern, PA	MAb	rheumatoid arthritis (see also digestive)	Phase III
CD40 ligand antibody	Biogen Cambridge, MA	MAb	lupus, immune thrombocytopenic purpura	Phase II
clenoliximab	IDEC Pharmaceuticals San Diego, CA SmithKline Beecham Philadelphia, PA	MAb	rheumatoid arthritis	Phase II
ConXn™ relaxin	Connetics Palo Alto, CA	recombinant soluble receptor	sclerodema	Phase II
Enbrel tumor necrosis factor (TNF) receptor	Immunex Seattle, WA Wueth-Ayerst Laboratories Philadelphia, PA	recombinant soluble receptor	rheumatoid arthritis	Phase III
h5G1.1	Alexion . Pharmaceuticals New Haven, CT	MAb	lupus, rheumatoid arthritis	Phase I/II
IDEC-131 humanized MAb	IDEC Pharmaceuticals San Diego, CA	MAb	systemic lupus erythematosus	Phase I
IL-2 fusion protein DAB $_{385}$ IL-2	Seragen Hopkinton, MA	fusion protein	rheumatoid arthritis (see also cancer, skin)	Phase I/II

interleukin-10 (IL-10)	Schering-Plough Madison, NJ	interleukin	rheumatoid arthritis (see also AIDS/HIV, digestive, heart, neurologic, respiratory, skin)	Phase II
IR 501 therapeutic vaccine	Immune Response Corp. Carlsbad, CA	vaccine	rheumatoid arthritis	Phase II
ISIS 2302	Isis Pharmaceuticals Carlsbad, CA	antisense	rheumatoid arthritis (see also digestive, skin, transplantation)	Phase II

AUTOIMMUNE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
MDX-33	Medarex Annandale, NJ	MAb	Autoimmune diseases, idiopathic thrombocytopenic purpura	Phase I
ORTHOCLONE OKT-4A	Ortho Biothech Rarian, NJ	MAb	treatment of CD4-mediated autoimmune diseases (see also transplantation)	Phase II
Quadrakine interleukin-4 (IL-4)	Schering-Plough Madison, NJ	interleukin	rheumatoid arthritis	Phase I
SMART™ Anti-CD3 HuM291	Protein Design Labs Mountain View, CA	MAb	autoimmune diseases (see also transplantation)	Phase I

BLOOD DISORDERS

Product Name	Company	Product Category	Indication	Development Status
CPC-111	Cypros Pharmaceuticals Carlsbad, CA	cellular therapy	sickle cell disease (see also heart)	Phase II
Factor VIII	Transkaryotic Therapies Cambridge, MA	gene therapy	hemophilia A	Phase I
GA-EPO	Hoechst Marion Roussel Kansas City, MO Transkaryotic Therapies Cambridge, MA	erythropoietin	anemia associated with chronic renal failure	Phase II
Kogenate-N tFVIII	Bayer Berkeley, CA	clotting factor	hemophilia A	Phase III

NovoSeven® recombinant factor VIIa	Novo Nordisk Pharmaceuticals Princeton, NJ	clotting factor	treatment of hemophilia A&B with and without antibodies against factors VIII/IX	Phase III
Optro™ recombinant human henoglobin (rHb1.1)	Somatogen Boulder, CO	recombinant human hemoglobin	oxygen-carrying agent and alternative to red blood cell transfusion	Phase II
			stimulation of red blood cell formulation	Phase I
ReFacto® recombinant factor VIII	Genetics institute Cambridge, MA	clotting factor	hemophilia A	Phase III
YM-337 MAb	Yamanouchi USA White Plains, NY Protein Design Labs Mountain View, CA	MAb	platelet aggregation	Phase I

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
1311-chTNT-1/B	Techniclone Tustin, CA	MAb	malignant glioma	Phase I
Aastrom™ Cell Production System stern and progenitor cell expansion from bone marrow and umbilical cord blood	Aastrom Biosciences Ann Arbor, MI	cellular therapy	cancer immunosuppression/ blood and immune system recovery for patients receiving ablative chemotherapy	Phase II
Actimmune® interferon gamma-1b	National Cancer Institute Bethesda, MD Genentech S. San Francisco, CA	interferon	colon, lung, ovarian, prostate cancers, melanoma	Phase II NCI Trial
AFP-Scan ™ technetium-99m-Fab' fragment (germ cell)	Immunomedics Morris Plains, NJ	MAb	extent of disease staging of liver and germ cell cancers	Phase II
allogeneic hematopoietic stem cell transplantation	SyStemix Palo Alto, CA	cellular therapy	advanced leukemia, lymphoma, myelodysplastic syndromes	Phase I

Allovectin-7 DNA/lipid complex encoding HLA-B7 antigen	Vical San Diego, CA	gene therapy	advanced metastatic melanoma, non-resectable squamous cell carcinoma of the head and neck	Phase II
ALT (autolymphocyte therapy)	Cellcor Newton, MA CYTOGEN Princeton, NJ	cellular therapy	metastatic renal cell carcinoma (kidney cancer)	Phase III completed
ALVAC-B7.1	National Cancer Institute Bethesda, MD	gene therapy	melanoma	Phase I NCI Trial
ALVAC-CEA-B7.1	National Cancer Institute Bethesda, MD	gene therapy	advanced adenocarcinomas	Phase I NCI Trial
ALVAC-CEA vaccine	National Cancer Institute Bethesda, MD	vaccine	advanced cancers	Phase I NCI Trial
ALVAC-IL-12 vaccine	National Cancer Institute Bethesda, MD Pasteur Merieux Connaught Lyons, France	vaccine	melanoma	Phase I NCI Trial
Ampligen®	Hemispherx Bioplama New York, NY	interferon	renal cancer (see also AIDS/HIV, infectious diseases, other)	Phase I/II
anti-cancer T-Cell gene therapy	Cell Genesys Foster City, CA	gene therapy	colon cancer	Phase I/II
anti-idiotype monoclonal antibody	Novartis Pharmaceuticals East Hanover, NJ	MAb	cancer	Phase I

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
anti-Tac(Fv)-PE38 immunotoxin	National Cancer Institute Bethesda, MD	MAb + toxin	leukemia, lyphoma	Phase I NCI Trial
anti-transferrin receptor MAb	National Cancer Institute Bethesda, MD	MAb	advanced, refractory solid tumors	Phase I NCI Trial
anti-VEGF humanized MAb	Genentech S. San Francisco, CA	MAb	cancer	Phase I

autologous hematopoietic stem cells for autologous hematopoietic transplantation	SySternix Pala Alto, CA	cellular therapy	hematopoietic reconstitution in patients with multiple myeloma, non-Hodgkin's lymphoma, breast cancer	Phase I/II
autologous peptide-specific activated lymphocytes	National Cancer Institute Bethesda, MD	cellular therapy	advanced solid tumors	Phase I NCI Trial
autologous transduced CD34+ bone marrow and peripheral blood stem cells	National Cancer Institute Bethesda, MD	gene therapy	breast cancer, myeloma	Phase I NCI Trial
Avicidin® MAb conjugate	MAb	colorectal, lung, prostate cancers	colorectal, pancreatic cancers	Phase II
Avicine ™ CTP-37	AVI BioPharma Portland, OR	vaccine	colorectal, pancreatic cancers	Phase II
Avonex® interferon beta-1A	Biogen Cambridge, MA	interferon	glioma (see also neurologic)	Phase II
B7 transfected allogeneic melanoma cell vaccine	National Cancer Institute Bethesda, MD	vaccine	melanoma	Phase I NCI Trial
BEC2, anti-idiotype MAb	ImClone Systems Somerville, NJ	vaccine	melanoma, small-cell lung cancer	Phase I
Betaseron® recombinant beta interferon-1b	National Cancer Institute Bethesda, MD Berlex Laboratories Wayne, NJ	interferon	non-small-cell lung cancer (see also neurologic)	Phase III NCI Trial
bispecific antibody	Chiron Emeryville, CA	MAb	cancer	Phase I
C225, anti-EGFR chimeric MAb	ImClone Systems Somerville, NJ	MAb	epidermal growth factor receptor positive cancers	Phase II
Campath 1H	LeukoSite Cambridge, MA	MAb	chronic lymphocytic leukemia	In clinical trials

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
carcinoembryonic antigen peptide-1 vaccine	National Cancer Institute Bethesda, MD	vaccine	brest, gastrointestinal tract, lung cancer	Phase I NCI Trial
CEACide™ humanized anti0CEA antibody (hMN14)	Immunomedics Morris Plains, NJ	MAb	colorectal cancer	Phase II

CEA-Scan™ technetium-99m-arcitumomab (breast)	Immunomedics Morris Plains, NJ	MAb	extent of disease staging of breast cancer	Phase II
CEA-Scan™ technetium-99m-arcitumomab (lung)	Immunomedics Morris Plains, NJ	MAb	extent of disease staging of lung cancer	Phase III
CEAVac™ anti-idiotype antibody vaccine	Titan Pharmaceuticals S. San Francisco, CA	vaccine	colorectal cancer	Phase II
cell therapy	CytoTherapeutics Providence, RI	cellular therapy	cancer pain, untreatable/unrelieved by other forms of treatment	Phase II
Cereport™ (RMP-7) and carboplatin	Alkermes Cambridge, MA		recurrent malignant brain tumor	Phase III
chemotherapy-resistant bone marrow	Genetix Rye, NY	gene therapy	treatment of cancer patients requiring chemotherapy	Phase I/II
chimeric MAb 14.18	National Cancer Institute Bethesda, MD	MAb	melanoma, neuroblastoma	Phase II NCI Trial
CM 101	CarboMed Brentwood, TN		cancer	Phase I/II
CMA-676	Wyeth-Ayerst Laboratories Philadelphia, PA	MAb	relapsed acute myelogenous leukemia	Phase II/III
CMB-401	Wyeth-Ayerst Laboratories Philadelphia, PA	MAb	ovarian cancer	Phase I/II
colon cancer cell line vaccine	Immune Response Corp. Carlsbad, CA Sidney Kimmel Cancer Center San Diego, CA	vaccine	colon cancer	Phase I
CP-358,774	OSI pharmaceuticals Uniondale, NY Pfizer New York, NY	cellular therapy	cancer	Phase I
CT-2584	Cell therapeutics Seattle, WA		ovarlan, prostate cancer, sarcoma	Phase I
cytosine deaminase gene-adenoviral vector	GenVec Rockville, MD	gene therapy	colon cancer	Phase I

CANCER AND RELATED CONDITIONS

Product Name	Company	Pr duct Category	Indication	Development Status
DA/Hu(gamma).4 (hIFN-XV) Retrovector ™ hIFN-y retroviral vector	Chiron Viagene San Diego, CA	gene therapy	metastatic melanoma	Phase I
DA/Hu(gamma).15-transduced autologous tumor cells and interferongamma expressing trasduced autologous tumor cells (combination therapy)	Chiron Viagene San Diego, CA	gene therapy	stage IV malignance melanoma	Phase I
DA/Hu(gamma).15-transduced autologous tumor cells; ITAT	Chiron Viagene San Diego, CA	gene therapy	disseminated malignant melanoma	Phase I
daniplestim	Searle Skokie, IL	growth factor	mobilization of peripheral blood stem cells	Phase III
dendritic cell therapy	Dendreon Mountain View, CA	cellular therapy	advanced prostate cancer	Phase II/III
			multiple myeloma	Phase I
E/A lipid complex (tgDCC-E/A)	Targeted Genetics Seattle, WA	gene therapy	breast, head and neck, ovarian cancers	Phase I
EGF fusion protein DAB $_{389}$ EGF	Seragen Hopkinton, MA	fusion protein	non-small-cell lung cancer'	Phase I/II
EPREX® erythropoietin	National Cancer Institute Bethesda, MD Ortho Biotech Raritan, NJ	erythropoietin	neuroblastoma	Phase II NCI Trial
ERB-38 immunotoxin fusion protein (recombinant)	National Cancer Institute Bethesda, MD	fusion protein	advanced stage solid tumors	Phase I NCI Trial
Ewing's sarcoma and alveolar rhabdomyosarcoma peptide vaccine	National Cancer Institute Bethesda, MD	vaccine	sarcoma	Phase I NCI Trial
FLT3 ligand	National Cancer Institute Bethesda, MD Immunex Seattle, WA	growth factor	melanoma, renal cell cancer	Phase I NCI Trial
G3139	Genta San Diego, CA	antisense	cancer	Phase I

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a single crystal of a pharmaceutically-acceptable crystal lattice component; and

an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

2. A pharmaceutical material comprising:

a mixture of single crystals, each crystal comprising a pharmaceutically-acceptable crystal lattice component and an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

3. The pharmaceutical material of claim 2 in which the crystals comprise at least two crystal lattice components, the first crystal lattice component being characterized by first pharmacokinetics and the second crystal lattice component being characterized by second pharmacokinetics.

4. The pharmaceutical material of claim 2 in which said mixture comprises a mixture of two different types of said crystals, the first type of the crystals comprising a first crystal lattice component and the second type of the crystals comprising at least one crystal lattice component different from the first crystal lattice component.

5. The pharmaceutical material of any of claims 2 to 4 in which the active pharmaceutical ingredient comprises discrete units and the units are included within the crystals in isolation from one another.

6. The pharmaceutical material of any of claims 2 to 5 in which the active pharmaceutical ingredient is included within the crystal at a concentration of about 0.001 to 1 weight percent based on the weight of the crystal including the active pharmaceutical ingredient.

7. A method of preparing a pharmaceutical product which comprises:

including an active pharmaceutical ingredient into single crystals of a pharmaceutically-acceptable crystal lattice component, the including being

conducted under pharmaceutically-acceptable conditions to provide the active pharmaceutical ingredient in the crystals in a growth-sector specific orientation; and

harvesting the single crystals.

8. The method of claim 7 and which further includes dissolving the harvested crystals into a pharmaceutically-acceptable diluent to form a solution containing the pharmaceutical free of the crystals.

9. A method of stabilizing an active pharmaceutical ingredient which comprises including the active pharmaceutical ingredient into single crystals of a pharmaceutically-acceptable crystal lattice component, the including being conducted under pharmaceutically-acceptable conditions to provide the active pharmaceutical ingredient in the crystals in a growth-sector specific orientation, the active pharmaceutical ingredient comprising discrete units and the units being included in the crystals in isolation from one another.

10. A method of administering an active pharmaceutical ingredient which comprises administering to a patient a pharmaceutical composition comprising single crystals of a pharmaceutically-acceptable crystal lattice component and an active pharmaceutical ingredient different from and included within the crystal lattice component in a growth-sector specific orientation, the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure.

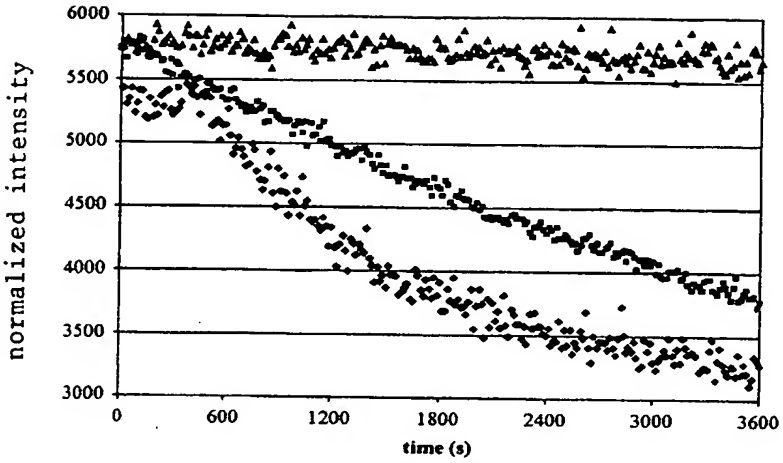
11. The invention of any of claims 1 to 10 in which, for each crystal, the active pharmaceutical ingredient is included within the crystal in a growth-sector specific orientation.

12. The invention of any of claims 1 to 11 and further comprising a pharmaceutically-acceptable adjuvant selected from the group consisting of excipients, diluents, carriers and mixtures thereof.

13. The invention of any of claims 1 to 12 in which the active pharmaceutical ingredient is a biopharmaceutical.

14. The invention of any of claims 1 to 13 in which the crystal lattice component is selected from the group consisting of: sucrose, lactose, trehalose, maltose, galactose, sorbose, mannitol, lactitol, sorbitol, glycine, alanine, lysine,

arginine, ascorbic acid, nicotinamide, thiamine, adenine, pyridoxine hydrochloride, caffeic acid, vanillic acid, ferulic acid, benzoate, sorbate, methyl paraben, sodium ascorbate, sodium saccharin, potassium citrate, zinc, calcium, and any derivatives, salt forms, or mixtures thereof.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time (s)

FIG. 1

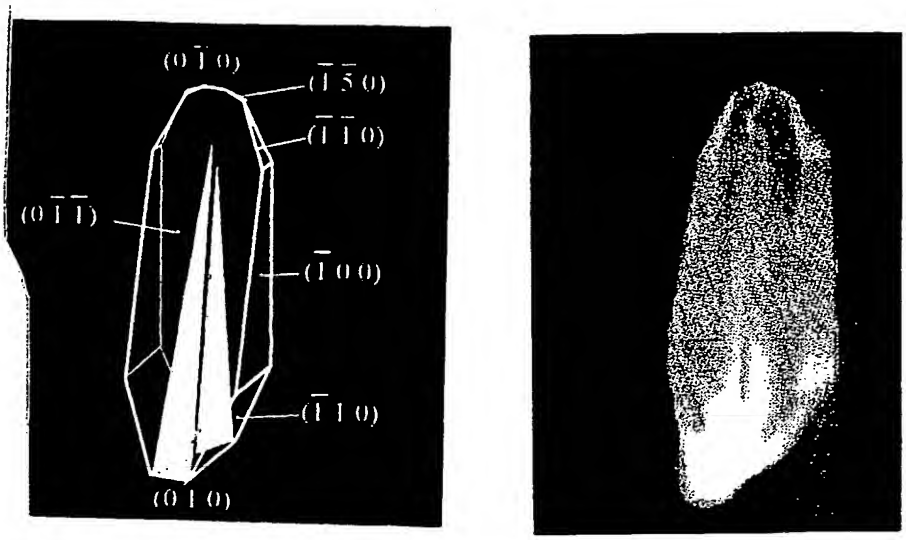

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16140

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 21838 A (ERIDANIA BEGHIN-SAY,FR) 19 June 1997 (1997-06-19) claims page 10, line 3 - line 18	1,7,10, 12-14
A	EP 0 119 480 A (BASF) 26 September 1984 (1984-09-26) claims	1-14
A	EP 0 314 469 A (FUJITSU LTD.,JP) 3 May 1989 (1989-05-03) claims	1-14
A	EP 0 435 450 A (ICI AMERICAS) 3 July 1991 (1991-07-03) cited in the application claims	1-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 December 2000	13/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 160 100 A (SANDOZ) 18 December 1985 (1985-12-18) claims	1-14
A	EP 0 629 393 A (ICI AMERICAS) 21 December 1994 (1994-12-21) claims	1-14

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/16140

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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The compositions are formulated in one embodiment as a unit dosage form. The term "unit dosage form" refers to physically discrete units, such as tablets, capsules, and suspensions in vials or cartridge/pen systems suitable as unitary dosages, particularly as unitary daily dosages. Each discrete unit contains a predetermined quantity of active pharmaceutical material calculated to produce the desired effect, e.g., a prophylactic or therapeutic effect. The amount of active pharmaceutical ingredient contained in a given dosage unit can be varied depending on the manner of delivering the crystals. For example, a single dosage unit in tablet form may contain 1/4, 1/3, 1/2 or 1 times the unit dose for the active pharmaceutical ingredient, according to which 1 to 4 tablets would be administered to achieve a unit dose of the active pharmaceutical ingredient.

Therefore, in one aspect of the present invention, there is provided a pharmaceutical product in dosage form comprising a pharmaceutical delivery unit including a dosage amount of active pharmaceutical ingredient. The API is contained within the crystal lattice component, and a sufficient amount of crystals is included within the delivery unit to constitute the dosage amount of the API. It will be appreciated that the dosage amount of pharmaceutical may be obtained by provision of one or more crystals of the present invention. One form of the product consists essentially of a dosage amount of the crystals. In an alternative form, the pharmaceutical product consists of the dosage amount of the crystals.

The ultimate delivery forms may include, for example, tablets, soft and hard gelatin capsules, pellets, granules, marumes, lozenges, sachets, cachets, elixirs, suspensions, ointments, suppositories, injection solutions and suspensions, nonpareils, spheres and sterile packaged powders. The crystals may be coated or uncoated, and may be combined with various pharmaceutical adjuvants, including excipients, diluents and carriers, as already described. One preferred form of the pharmaceutical product consists essentially of the crystals, and an alternate form consists of the crystals and the pharmaceutically-acceptable adjuvants. The delivery forms are prepared by conventional techniques such as disclosed in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Company, Easton, PA (1995), which is incorporated herein by reference, or other treatises available to the skilled artisan.

Compressed tablets, for example, are prepared by well-known means which are conventional in the art. The tablets may be prepared by wet or dry granulation methods or by direct compression, and may be produced by any of a wide variety of tabletting machines. Tablet formulations usually incorporate diluents, binders, lubricants and disintegrators, as well as the crystals with included API's. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride, and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin, and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

Certain solid pharmaceutical dosage forms of the present invention, most notably tablets, may be coated in conventional fashion with a wide variety of materials utilizing various processes. Typically, the products of the present invention may be sugar coated or film coated in accordance with well-known techniques. The coatings serve an aesthetic purpose as well as a practical one. Coatings can mask an unpleasant taste or odor, can increase ease of ingestion by the patient, and can serve to improve the ultimate appearance of the dosage form. Similarly, coatings can protect the product from the effects of air, moisture and light, can improve product identification, and can facilitate handling in packaging and fill lines during manufacture.

Various adjuvants may be included in the coating formulations as is well known in the art. These include, for example, permeability enhancers, plasticizers, antitacking agents and the like. A discussion of coating techniques and adjuvants is presented in United States Patent No. 5,015,480, issued to Childers et al. on May 14, 1991, the pertinent portions of which are hereby incorporated herein by reference. Further information pertinent to coating processes and equipment may be obtained from Remington's Pharmaceutical Sciences, supra.

Tablets are often coated with sugar as a flavorant and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets by using large amounts of

pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the subject consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some subjects.

A lubricant is used in a tablet formulation to prevent the tablet and punches from sticking in the die of the tabletting machine. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the crystals. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are used to protect crystals and the included API's from the strongly acidic contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acidic environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

The crystals with included API's may similarly be formulated into capsules for administration. Such capsules are prepared utilizing conventional encapsulating methods. A general method of manufacture involves preparing the crystals for use in capsules, such as by milling the crystals to a suitable size. The crystals are blended with desired excipients, diluents or carriers, and the resulting mixture is filled into suitably-sized capsules, typically hard gelatin capsules, using conventional capsule-filling machines. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

When it is desired to administer the crystal formulations as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which

may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are also in wide use.

The crystals can also be similarly formulated as elixirs or suspensions for convenient oral administration or for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes.

The inventive crystals enable the design of sustained-release formulations based upon various factors to yield both the desired amount of active pharmaceutical ingredient and the desired pharmacokinetic profile for delivery of the active pharmaceutical ingredient. Selectively incorporating the active pharmaceutical ingredient into the crystal lattice, e.g., into a specific crystal growth sector, modulates the release profiles and can therefore be used to effect desired pharmacological properties. The choice of the crystal component and the process used to grow the crystals of excipient host and guest active pharmaceutical ingredient can be selected and/or modified to adjust parameters such as the delivery rate of the active pharmaceutical ingredient upon use of the formulation. The active pharmaceutical ingredient is incorporated into the crystal matrix at a selected rate, typically as only a small weight percentage of the overall crystal. This permits moderate and uniform rates of release.

Various approaches may be used to accomplish a delayed or sustained release of active pharmaceutical ingredient from the crystals. In a typical application the crystals of the desired size are combined with a compatible preservative and the mixture is injected subcutaneously or surgically implanted to provide a prolonged payout as the crystals dissolve as a result of contact with the surrounding body tissue and fluid. In one approach, the concentration of the active pharmaceutical ingredient in the crystals is reduced in order to effect a sustained release over time. Alternatively, larger crystals may be used to provide for more prolonged payout of the active pharmaceutical ingredient. In another approach, coatings on the crystals are used to affect the rate of release of the active pharmaceutical ingredient. Such coatings may comprise the same crystal lattice component but without the included active pharmaceutical ingredient, as well as other coating compositions useful for this purpose.

In the alternative, the crystals of the present invention can be used to isolate and/or store the active pharmaceutical ingredient for later reconstitution into solution. The crystals may be stored for extended periods of time prior to reconstitution in view of the added stability accorded the API's by the encompassing crystal lattice component. The crystals are then combined with pharmaceutically-acceptable excipients, diluents or carriers to prepare the solutions for subsequent administration. The crystals are readily dissolved or suspended in appropriate diluents, which may be selected, for example, from the list previously provided with regard to diluents used to initially prepare the crystals.

Such solutions of dissolved crystals provide the active pharmaceutical ingredient free of the previously encompassing crystal lattice component. The solutions are useful, for example, for oral administration, parenteral use, or as suppositories. For parenteral administration, for example, the crystals may be formulated in a pharmaceutically-acceptable diluent such as physiological saline (0.9%), 5% dextrose, Ringer's solution, and the like, along with other additives to reduce the solubility of the crystals in suspension.

The resulting pharmaceutical formulations provide an active pharmaceutical ingredient which is included within the host crystal and has enhanced stability and shelf-life. The present invention therefore satisfies the desire to provide certain pharmaceuticals having an acceptable, room-temperature shelf-life. Depending on the circumstances, particularly the API involved, the desired shelf-life can be as little as one month, or may be at least one year, two years or more. The pharmaceutical molecules are generally isolated from one another and from the environment by the surrounding crystal lattice. The containment of the API in the solid crystal lattice also fixes the conformational orientation. This eliminates most of the potential degradation mechanisms, such as polymerization, oxidation, deamidation and proteolysis, that could otherwise reduce the stability of the pharmaceutical.

Methods demonstrating stability include but are not limited to high-performance liquid chromatography for purity and potency, FT-IR for secondary structure, in-vitro and in-vivo bioassays, and pharmacokinetic profiles.

The crystals of the present invention are readily prepared and are useful in containing the included API in an isolated, oriented position within the lattice. The utility of the present invention is demonstrated in the following examples, which are illustrative in nature, and are not to be considered limiting of the scope of the present invention.

Example 1

To demonstrate the potential kinetic stabilization of proteins, green fluorescent protein (GFP) was incorporated into deionized α-lactose monohydrate. GFP was selected because it is known to fluoresce only in its native conformation. Upon denaturation, the interior of the β-barrel of the molecule is exposed and the fluorescence of the p-hydroxybenzylideneimidazolinone chromophore is rapidly quenched. Typical crystal growth conditions involved the addition of 8 volumes of an approximately 1 mg/mL (approximately 37 μmole) solution of GFP in 10 mM tris-HCl, pH8 and 10 mM EDTA to 100 volumes of a supersaturated aqueous solution (approximately 1.15 M) of deionized α-lactose monohydrate. The mixed solution was allowed to stand for 3-4 days at room temperature in a 24-well plate. Crystals were harvested between 1-3 days and displayed a hatchet morphology as shown in Figure 1 with a broad base (010) further bounded by {100}, {110}, {1-10}, and {0-11}. Small (0-10) and {1-50} faces are also occasionally present. When illuminated with a long wavelength UV lamp, the crystals exhibited a bright green fluorescence localized within a sharply defined pyramid corresponding to the (010) growth sector. This indicates that GFP is selectively recognized and overgrown by the (010) face in preference to the others. More importantly, it is evidence that the GFP is in its native conformation. The level of GFP to lactose is approximately 0.008% (w/w).

GFP fluorescence intensity was measured as a function of time and temperature in three environments: saturated aqueous α-lactose solution, lyophilized α-lactose, and crystalline α-lactose monohydrate. As shown in Figure 2, both the solution and lyophilized preparations lost nearly half of the fluorescence intensity at 333°K within one hour. The crystal showed no change at 333°K or even 343°K.

Example 2

To investigate the potential for incorporation of a biopharmaceutical into crystals of biocompatible excipients, studies were conducted using rhodamine-labeled glandular glucagon and lactose. As in the previous studies, the rhodamine label was used to facilitate the visualization of glucagon in the host crystals. Typical crystal growth conditions involved the addition of 5 volumes of a supersaturated solution of deionized α-lactose monohydrate to 1 volume of an approximately 1.5 mg/mL (approximately 300 to 400 μmole) of rhodamine-labeled glucagon in purified water. The mixed solution was allowed to stand at room temperature in a 24-well plate. Crystals were harvested between 1-3 days and displayed a hatchet morphology with a broad base. With the rhodamine label, glucagon inclusion was visible in the crystals as a well-defined pyramid corresponding to the (010) growth sector. The level of inclusion was determined to be approximately 0.1% (w/w).

In-vitro dissolution experiments were performed on the glucagon/lactose crystals to evaluate potential for in-vivo, sustained-release pharmacokinetics. The release of rhodamine-labeled glucagon into solution was followed by fluorescence spectroscopy. In a typical experiment, 1-2 crystals were added to 100 microliters of phophate buffered saline solution at room temperature and the increase in fluorescence of the solution was monitored over time. The release of glucagon from the dissolving crystals was generally complete after 24-48 hours depending on crystal size and was linear until the last few hours of dissolution. Additional details are contained in the article entitled "Stabilization of Proteins in Single Crystal Hosts: Green Fluorescent Protein and α-Lactose Monohydrate," M. Kurimoto, P. Subramony, R. Gurney, S. Lovell, J.A. Chmielewski, B. Kahr, J. Am. Chem. Soc. 1999, 121, 6952-6953, which article is hereby incorporated herein by reference.

Example 3

To demonstrate the universality of this technology for incorporation of a diversity of biopharmaceuticals into crystals of biocompatible excipients, studies were conducted using biosynthetic human insulin and insulin analogs,

V8-GLP-1(7-37)OH, a glucagon-like insulinotropic peptide-1 analog, exendin, and human growth hormone in deionized α-lactose monohydrate or phthalic acid. Information regarding V8-GLP is available in United States Patent No. 5,705,483, issued to Galloway and Hoffman on January 6, 1998, which patent is hereby incorporated herein in its entirety. For information regarding exendin, see, e.g., R. Goke, H.C. Fehmann, T. Linn, H. Schmidt, M. Krause, J. Eng, B. Goke, "Exendin-4 is a High Potency Agonist and Truncated Exendin-(9-39)-amide an Antagonist at the Glucagon-like Peptide 1-(7-36)-amide Receptor of Insulin-secreting Beta-cells," J. Biol. Chem. 1993, Sep 15, 268(26), pp. 19650-5, which reference is hereby incorporated herein in its entirety.

Typical crystal growth conditions involved the addition of 1 volume of an approximately 10 mg/mL rhodamine- or Texas red-labeled peptide or protein in 0.1M phosphate-buffered saline solution (PBS, pH7.4) to 10 volumes of a supersaturated α-lactose solution or phthalic acid solution. Supersaturated solutions of purified α-lactose were obtained by adding 0.41 grams of α-lactose to 1 mL of purified water, allowing to dissolve in a 50-70°C water bath, and cooling to room temperature. Supersaturated solutions of phthalic acid were prepared by adding 0.05 grams of phthalic acid to 1 mL of either 70/30 (v/v) water/acetonitrile or 90/10 water/ethanol, allowing to dissolve in a 50-70°C water bath, and cooling to room temperature. Larger volumes of supersaturated solutions are obtained by using the same solute-to-solvent ratio.

The solutions of labeled peptide or protein with the supersaturated α-lactose or phthalic acid were mixed by swirling, transferred to a 24-well crystallization plate or other suitable glass or polypropylene container, and allowed to stand at room temperature. Crystals were harvested in 4-5 days and rinsed with hexanes, ethanol, or methanol. All preparations yielded crystals with dye-labeled protein inclusions as determined by microscopic examination using an Olympus SZ-40 microscope with a CCD vision camera.

The shape of the crystals formed was dependent on the solvent system used for the phthalic acid. The crystals formed with phthalic acid in water/ethanol were long, petal-shaped clusters. The crystals formed with water/ethanol were smaller

and rhombic. Crystals of labeled-insulin/lactose were dissolved in PBS and analyzed by HPLC. The level of insulin inclusion was determined to be approximately 0.1%. This process is scalable from 100 µL to several liters. The larger volume crystallizations were performed using glass beakers, or other appropriate large containers, covered with watch glasses.

Using the same process, unlabeled insulin and exendin have also been incorporated into α-lactose monohydrate and phthalic acid crystals. Upon dissolution of the crystals with 0.01N HCl, purified water and/or methanol, the level of peptide included in these hosts was determined by analysis of the sample solutions with an HPLC system in the flow-injection analysis mode using a chemiluminescent nitrogen-specific detector (CLND). The level of peptide inclusions ranged from approximately 0.1% to 10% (w/w). These data demonstrate that the level of inclusion can be manipulated by appropriate choice of guest and host molecules in addition to crystallization conditions. See also the following references which are hereby incorporated herein in their entirety: M. Windholz, (editor). Merck Index, 10^{th} edition, p. 769; R.A. Visser, Neth. Milk Dairy Journal, **34**, 1980, pp. 255-275; J. Chmielewski, et al., JACS, **119**, 43, pp. 105665-10566.

NeuroCell™-PD (cellular transplantation therapy)	Diacrin Charlestown, MA Genzyme Tissue Repair Cambridge, MA	cellular therapy	Parkinson's disease	Phase II
neurotrophin-3	Amgen Thousand Oaks, CA Regeneron Pharmaceuticals Tarrytown, NY	growth factor	enteric neuropathies	Phase I/II
pimagedine	Alteon Ramsey, NY Genentech S. San Francisco, CA		overt neuropathy (see also diabetes)	Phase III
prosaptide TXI4(A)	Myelos Neurosciences San Diego, CA	growth factor	neuropathic pain and peripheral neuropathy	Phase II

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Rebif® recombinant	Serono Laboratories Norwell, MA	interferon	relapsing, remitting multiple sclerosis; transitional multiple sclerosis (see also cancer, infectious disease)	application submitted
ReoPro® abciximab	Centocor Malvern, PA Eli Lilly Indianapolis, IN	MAb	stroke (see also heart)	Phase II
Spheramine™	Titan Pharmaceuticals S. San Francisco, CA	cellular therapy	Parkinson's disease	Phase I
Zenapax® daclizumab	Hoffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	tropical spastic paraparesis (model for multiple sclerosis) (see also cancer, eye, skin, transplantation)	Phase I/II

RESPIRATORY DISEASES

Product Name	Company	Product Category	Indication	Development Status
AAV CFTR gene therapy	Targeted Genetics Seattle, WA	gene therapy	sinusitis (see also genetic)	Phase I
acellular partussis vaccine	Chiron Emeryville, CA	vaccine	pediatric pertussis (whooping cough)	application submitted
anti-igE humanized MAb	Genentech S. San Francisco, CA Novartis Pharmaceuticals East Hanover, NJ Tanox Biosystems	MAb	allergic asthma	Phase III

			allergic rhinitis	Phase II
influenza rHAO Vaccine influenza vaccine	Protein Sciences Meriden, CT	vaccine	prevention of influenza	Phase II
influenza virus vaccine (live, attenuated)	Aviron Mountain View, CA	vaccine	prevention of influenza	Phase III
interleukin-4 receptor	Immunex Seattle, WA	recombinant soluble receptor	asthma	Phase I
interleukin-10 (iL-10)	Schering-Plough Madison, NJ	interleukin	acute lung injury (see also AIDS/HIV, autoimmune, digestive, heart, neurologic, skin)	Phase I
lisofylline	Cell Therapeutics Seattle, WA		acute lung injury (see also other)	Phase II
NEUPOGEN® Filgrastim (rG-CSF)	Amgen Thousand Oaks, CA	colony stimulation factor	multilobar pneumonia, pneumonia sepsis (see also AIDS/HIV, cancer)	Phase III

RESPIRATORY DISEASES

Product Name	Company	Product Category	Indication	Development Status
Oxsodrol® rhCu2r super dismutase	Bio-Technology General Iselin, NJ	dismutase	bronchopulmonary dysplasia in premature infants	Phase III
parainfluenza type-3 vaccine (live, attenuated bovine)	Aviron Mountain View, CA	vaccine	prevention of parainfluenza type-3 infection (cause of croup in infants)	Phase II
PIV vaccine, live attenuated	Wyeth-Lederle Vaccines & Pediatrics Philadelphia, PA	continuous cell line vaccine	prevention of parainfluenza virus-mediated lower respiratory disease in infants	Phase I
Quillmmune-F	Aquila Biopharmaceuticals Worcester, MA	vaccine	pneumococcal infections in the elderly	Phase II
recombinant platelet activating factor-acetylhydrolase (rPAF-AH)	ICOS Bothell, WA		acute respiratory distress syndrome, asthma (see also digestive)	Phase II

RSV subunit vaccine	Wyeth-Lederle Vaccines & Pediatrics Philadelphia, PA	continuous cell line vaccine	prevention of respiratory syncytial virus-mediated lower respiratory disease in the elderly and at-risk children	Phase II
RSV vaccine, live, attenuated	Wyeth-Lederle Vaccines & Pediatrics Philadelphia, PA	continuous cell line vaccine	prevention of respiratory syncytial virus-mediated lower respiratory disease in infants	Phase I
soluble ICAM-1 (BIRRA)	Boehringer Ingelheim Pharmaceuticals Ridgefield, CT	recombinant soluble receptor	prevention and/or treatment of rhinovirus-induced common cold	Phase II
Synagis™ MEDI-493 humanized RSV MAb	Medimmune Gaithersburg, MD	MAb	prevention of respiratory syncytial virus disease	application submitted
TP10	T Cell Sciences Needham, MA	recombinant soluble receptor	acute respiratory distress syndrome (see also heart, transplantation)	Phase II
truncated ICAM	Bayer Berkeley, CA	adhesion molecule	rhinovirus-associated exacerbations of asthma	Phase I

SKIN DISORDERS

Product Name	Company	Product Category	Indication	Development Status
anti-CD11a humanized MAb (hu1124)	Genentech S. San Francisco, CA XOMA Berkeley, CA	MAb	moderate to severe psoriasis	Phase II
gamma interferon	Connetics Palo Alto, CA	interferon	keloids	Phase II
ICM3	ICOS Bothell, WA	MAb	psoriasis	Phase I
IL-2 fusion protein DAB_{389} IL-2	Seragen Hopkinton, MA	fusion protein	moderate to severe psoriasis (see also autoimmune, cancer)	Phase I/II
interleukin-10 (IL-10)	Schering-Plough Madison, NJ	interleukin	psoriasis (see also AIDS/HIV, autoimmune, digestive, heart, neurologic, respiratory)	Phase I

IR 502 therapeutic vaccine	Immune Response Corp. Carlsbad, CA	vaccine	psoriasis	Phase II
ISIS 2302	Isis Pharmaceuticals Carlsbad, CA	antisense	psoriasis (see also autoimmune, digestive, transplantation)	Phase II
keratinocyte growth factor-2 (KGF-2)	Human Genome Sciences Rockville, MD	growth factor	wound healing (see also other)	Phase I
LFA3TIP	Biogen Cambridge, MA	recombinant T-cell inhibitor	psoriasis	Phase II
Regranex ™ becaplermin (recombinant human platelet-derived growth factor-BB)	Chiron Emeryville, CA R.W. Johnson Pharmaceutical Research Institute Raritan, NJ	growth factor	pressure ulcers (see also other)	Phase III
T4N5 Liposome Lotion T4 endonuclease V encapsulated in liposomes	Applied Genetics Freeport, NY		protection against actinic keratoses in patients with xeroderma pigmentosa	Phase III
TGF-beta3	OSI Pharmaceuticals Uniondale, NY	growth factor	impaired wound healing (see also other)	Phase II
transforming growth factor-beta-3	Novartis Pharmaceuticals East Hanover, NJ	growth factor	wound healing	Phase II
Zenapax® daclizumab	Hoffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	psoriasis (see also cancer, eye, neurologic, transplantation)	Phase I/II

TRANSPLANTATION

Product Name	Company	Product Category	Indication	Development Status
allogeneic hematopoietic stem cells	SyStemix Palo Alto, CA	cellular therapy	correct genetic diseases by in utero transplantation of genetically unaffected cells from a sibling or parent	Phase I
CBL antibody (ABX-CBL)	Abgenix Foster City, CA	MAb	graft versus host disease	Phase II
CTLA4lg	Bristol-Myers Squibb Princeton, NJ	recombinant soluble receptor	immunosuppression	Phase II

HSD-Tk retroviral vector	Genetic Therapy Gaithersburg, MD Systernix Palo Alto, CA	gene therapy	treatment of graft versus host disease in allogenetic hematopoietic stern cell transplantation	Phase I
HSV-tk	Chiron Emeryville, CA	gene therapy	graft versus host disease in bone marrow transplantation	Phase I
ISIS 2302	Isis Pharmaceuticals	antisense	renal transplant rejection (see also autoimmune, digestive, skin)	Phase II
LDP-01	LeukoSite Cambridge, MA	MAb	kidney transplantation (see also neurologic)	Phase I/II
MEDI-507 (humanized MAb)	Medimmune Gaithersburg, MD BioTransplant Charlestown, MA	MAb	graft versus host disease	Phase II
			acute kidney transplant rejection	Phase I/II
ORTHOCLONE OKT4A	Ortho Biotech Raritan, NJ	MAb	prevention of organ transplant rejection (see also autoimmune)	Phase II
Simulect basiliximab	Novartis Pharmaceuticals East Hanover, NJ	MAb	transplantation	application submitted
SMART™ Anti-CD3 HuM291	Protein Design Labs Mountain View, CA	MAb	organ transplantation (see also autoimmune)	Phase I
TP10	T Cell Sciences Needham, MA	recombinant soluble receptor	transplantation (see also heart, respiratory)	Phase I/II
Zenapax® daclizumab	Hoffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	liver transplantation (see also cancer, eye, neurologic, skin)	Phase II
			pediatric kidney transplantation	Phase I/II
Zenapax® daclizumab and Cellcept®	Hoffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	kidney transplant rejection, cyclosporine elimination	Phase I/II

OTHER

Product Name	Company	Pr duct Categ ry	Indication	Development Status
Recombumin recombinant human albumin	Centeon King of Prussia, PA		excipient use	Phase I

Regranex™ becaplurmin (recombinant human platelet-derived growth factor-BB)	Chiron Emeryville, CA R.W. Johnson Pharmaceutical Research Institute Raritan, NJ	growth factor	venous ulcers (see also skin)	Phase III
rhBMP-2	Genetics Institute Cambridge, MA	growth factor	bone and cartilage repair	in clinical trials
Saizen® somatropin (rDNA origin for injection	Serono Laboratories Norwell, MA	human growth hormone	chronic renal failure in children (see also growth disorders)	Phase III
			post-operative recovery	Phase II
Serostim™ somatropin (rDNA origin for injection	Serono Laboratories Norwell, MA	human growth hormone	metabolic conditions (see also cancer)	Phase II
Somatokine® recombinant insulin-like growth factor-V binding protein-3	Celtrix Pharmaceuticals Santa Clara, CA	growth factor	hip fractures, severe acute burns	Phase II
TGF-beta3	OSI Pharmaceuticals Uniondale, NY	growth factor	oral mucositis (see also skin)	Phase II

The content of this survey has been obtained through government and industry sources based on the latest information.
Survey current as of March 13, 1998. The information may not be comprehensive. For more specific information about a particular product, contact the individual company directly.

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In one aspect, particular benefit is obtained with this invention when used with biopharmaceuticals, which include, for example, any proteins, polypeptides, enzymes, immunoglobulins, polynucleic acids, and plasmids or other biopolymers. Specific examples of biopharmaceuticals to be included in the crystal formulations of the present invention include the following: insulin, glucagon, Glucagon-Like Peptide-1 (7-37)OH (GLP-1), human growth hormone, leptin, follicle-stimulating hormone (FSH), ribozyme, and analogs thereof .

The API's useful with the present invention include those which themselves may form crystalline products, as well as those which do not. By way of example, any proteins can be prepared as microcrystalline suspension products, but the results have frequently been unsatisfactory using existing technology. However, inclusion of these biomolecules into a host crystal system in accordance with the present invention overcomes this limitation on crystallization. The invention further finds utility even with API's that are readily crystallized, such as insulin. The incorporation of such API's into a single crystal lattice can be used to enhance stability or provide means of delivery that have different characteristics.

Solvents for preparation of the saturated and supersaturated crystal lattice component include, but are not limited to, water, alcohols (e.g., ethanol, isopropanol), other organic solvents, acids, bases, and buffers.

The crystals of the present invention are prepared to have a predetermined amount of active pharmaceutical ingredient. The desired amount of active pharmaceutical ingredient will depend on typical considerations, such as the effective amount of API used for administering to a patient. The concentration of API in the crystal is controlled, such as by previously described means, to yield crystals which are readily used in preparing pharmaceutical formulations for administration. The active pharmaceutical ingredient can be incorporated into the crystals at any of a wide variety of molar or weight percentages. Preferred percentages can be easily selected by a skilled artisan taking into account the usual considerations for later formulation of the desired pharmaceutical compositions, depending on the application, route of delivery, and desired pharmacological profile. Preferred percentages include, for example, concentrations of 0.01 - 1 weight percent. As used herein, all weight percentages are given as the percent

based on the weight of the crystal including the crystal lattice component, the active pharmaceutical ingredient and any other components included within the crystals, unless stated otherwise.

The crystals may be prepared at varying size distributions, similarly depending on the subsequent formulating to be done with the crystals, or on crystal growth parameters. The crystals may be harvested and then sorted directly to desired size ranges, or may first be processed, such as by grinding or milling, and then sorted such as by sieving. As will be appreciated, a desired amount of active pharmaceutical ingredient may be obtained simply by obtaining a determined weight of crystals containing the active pharmaceutical ingredient at a known weight concentration. The useful size or weight range of the crystals of the present invention accordingly varies widely, depending on such factors as the inclusion level of the active pharmaceutical ingredient, the dosage amount for the active pharmaceutical ingredient, and the method of delivery of the crystals. By way of example, suitable crystals may have an average size distribution of 1 μm to 1 mm .

The crystals of the present invention will typically be used in a formulation comprising a large number of crystals. It is a feature of the present invention that the active pharmaceutical ingredient is included within the crystal lattice component in a predictable, oriented fashion. This leads to a uniform concentration of the active pharmaceutical ingredient as a molar, and therefore weight, percentage of the crystals. In one aspect of the present invention, there is provided a composition of crystals having a substantially uniform weight concentration of active pharmaceutical ingredient as between crystals. The term "substantially uniform weight concentration" refers to the fact that the weight concentration of active pharmaceutical ingredient in the various crystals is sufficiently uniform that an acceptably accurate weight of active pharmaceutical ingredient can be obtained based on the weight of the crystals and the average concentration of active pharmaceutical ingredient in such crystals. In one preferred embodiment, there is provided a composition of crystals in which the size distribution of active pharmaceutical ingredient does not vary between crystals by more than about 20 percent. However, alternate embodiments may be equally

useful, including mixtures of different size crystals. A desired quantity of active pharmaceutical ingredient is then accurately obtained by measuring a weight amount of crystals which, given the concentration of active pharmaceutical ingredient, yields the selected weight of active pharmaceutical ingredient.

The crystals and included API's are useful in the crystal form for both the stabilization and storage of the API and for the administration of the API to a patient. As used herein, it will be appreciated that the term patient refers to either humans or non-humans, depending on the nature of the active pharmaceutical ingredient. The crystals may be used as such, and in one aspect of the present invention the crystals consist essentially of simply the crystal lattice component and the API. Alternatively, the crystals include the crystal lattice component and the API in combination with other pharmaceutically-acceptable adjuvants also contained within the crystals.

The crystals of the present invention are preferably formulated as pharmaceutical materials for ultimate delivery in solid or liquid form. In such applications, the crystals are typically formulated with common, compatible, pharmaceutically-acceptable adjuvants, such as excipients, diluents, carriers or mixtures thereof. For purposes herein, the term "pharmaceutically-acceptable" refers in this context to the excipients, diluents or carriers, as well as coatings or other components referred to elsewhere, being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Examples of excipients, diluents, and carriers that are suitable for such dosage forms are well known in the art, and include the following: suspension additives such as tonicity modifiers, buffers, precipitants, and preservatives; fillers and extenders such as starch, lactose, dextrose, sucrose, sorbitol, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol and glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid

polyethyl glycols. Additionally, the adjuvant may comprise crystals of the crystal lattice component that are prepared without the included API.

The crystals may be coated to achieve various effects. In one approach, the crystals are coated with the same crystal lattice component which forms the underlying crystal, but without the included API. This assures that the coating and the underlying crystal have compatibility. The coating is then applied at a thickness which provides the desired effect, such as further protection of the active pharmaceutical ingredient, bulking of the crystal for handling, and/or effecting a sustained or delayed release of the active pharmaceutical ingredient. Alternatively, the same effects can be accomplished by coating the crystals with other compatible coating compositions, such as those which are well known in the pharmaceutical coating art. The crystals can also be coated so as to release the active pharmaceutical ingredient only or preferably in a particular part of the intestinal tract or other route of administration, possibly over a period of time. This is accomplished, in known fashion, using coatings, envelopes, and protective matrices made, for example, from polymeric substances or waxes.

It is a feature of one aspect of the present invention that the crystals and included API's may be packaged and administered to patients in discrete pharmaceutical dosage forms. The crystals may be used as such in solid form, or may be formulated into liquid solutions or suspensions prior to use. The compositions may accordingly be administered by various routes, for example, by the oral, rectal, vaginal, ocular, buccal, nasal, pulmonary, iontophoretic, topical or parenteral routes. Such compositions form part of the present invention and are prepared in manners well known in the pharmaceutical art.

The API's of the present invention are effective over a varied dosage range. Such dosages are readily accommodated by the present invention by permitting various sizes of crystals, concentrations of API, etc. It will be understood that the amount administered will be determined in light of the relevant circumstances, including the condition to be treated, the choice of API to be administered, the size of the patient being treated, and the chosen route of administration. Therefore, specific dosage ranges will differ accordingly, and are not limiting of the scope of the invention in any way.

gamma interferon gene therapy	Chiron Emeryville, CA	gene therapy	cancer	Phase I

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Gastrimmune™ neutralizing G17 hormone	Aphton Woodland, CA	vaccine	colorectal, pancreatic, stomach cancers (see also digestive)	Phase I/II
GeneVax® gene vaccine	Centocor Malvern, PA	vaccine	colorectal cancer	Phase I
GLI-328	Genetic Therapy Galthersburg, MD	gene therapy	glioblastoma multiforme	Phase III
GM-CSF cellular cancer vaccine	Powderject Vaccines Madison, WI	vaccine	melanoma, sarcoma	Phase I
GMK garglioside antigen	Bristol-Myers Squibb Princeton, NJ Progenics Pharmaceuticals Tarrytown, NY	vaccine	prevent recurrence following surgery to remove primary melanoma	Phase III
gp100 adenovirus vaccine	National Cancer Institute Bethesda, MD Genzyme Molecular Oncology Cambridge, MA	vaccine	melanoma	Phase I NCL Trial
gp 100 peptide vaccine	National Cancer Institute Bethesda, MD	vaccine	melanoma	Phase I NCL Trial
GVAX™ cancer vaccine	Cell Genesys Foster City, CA	vaccine	prostate, lung cancers, melanoma	Phase I/II
HER-2/neu peptide vaccine	National Cancer Institute Bethesda, MD	vaccine	breast, colorectal, ovarian, prostate cancers	Phase I NCL Trial
Herceptin™ trastuzumab (anti-HER-2 humanized MAb)	Genentech S. San Francisco, CA	MAb	breast cancer	Phase III completed
HPV 16, E6 and E7 peptide vaccine	National Cancer Institute Bethesda, MD	vaccine	cervical cancer	Phase I NCL Trial
HPV E7 lipopeptide vaccine	National Cancer Institute Bethesda, MD Cytel San Diego, CA	vaccine	cervical cancer	Phase I NCL Trial

HPV vaccine	Medimmune Gaithersburg, MD SmithKline Beecham Philadelphia, PA	vaccine	cervical cancer (see also infectious diseases)	Phase I
HSPPC-96 (autologous tumor derived)	Antigenics New York, NY	hear shock protein	melanoma, pancreatic renal cell cancers	Phase I
human growth hormone	Transkaryotic Therapies Cambridge, MA	gene therapy	cancer cachexia (muscle wasting)	Phase I
IDEC-In88	IDEC Pharmaceuticals San Diego, CA	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II
IDEC-Y88	IDEC Pharmaceuticals San Diego, CA	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Leucotropin GM-CSF	Cangene Mississauga, Ontario	colony stimulating factor	mobilization of peripheral blood stem cells in patients with adjuvant breast cancer	Phase III
Leukine™ sargramostim (GM-CSF)	Immunex Seattle, WA	colony stimulating factor	prophylaxis and treatment of chemotherapy-induced neutropenia, prophylaxis of chemotherapy-induced neutropenia in acute myelogenous leukemia (see also AIDS/HIV)	application submitted
Leuvectin DNA/lipid complex encoding iL-2	Vical San Diego, CA	gene therapy	prostate cancer, renal cell carcinoma, melanoma, sarcoma	Phase I
LP 2307	LIDAK Pharmaceuticals La jolla, CA	vaccine	malignant melanoma	Phase I/II
LR-3001	Inex Pharmaceuticals Hayward, CA	antisense	chronic myelogenous leukemia in accelerated phase or blast crisis	Phase I
LYM-1	Techniclone Tustin, CA	MAb	lymphoma	Phase II/III
Lymphocide™ and CD22 humanized MAb	Immunomedics Morris Plains, NJ	MAb	non-Hodgkin's B-cell lymphoma	Phase I/II

LymphoScan™ technetium-99m-bectumomab (lymphoma)	Immunomedics Morris Plains, NJ	MAb	extent of disease staging of non-Hodgkin's B-cell lymphoma, detection of residual disease following radiation/chemotherapy	Phase III
MAb	Glaxo Wellcome Rsch. Triangle Park, NC	MAb	lung, prostate cancers	Phase II
MART-1 adenovirus vaccine	National Cancer Institute Bethesda, MD Genzyme Molecular Oncology Cambridge, MA	vaccine	melanoma	Phase I NCL Trial
MART-1 melanoma vaccine	National Cancer Institute Bethesda, MD	vaccine	metastatic melanoma	Phase I NCL Trial
MD Rx1™	Titan Pharmaceuticals S. San Francisco, CA	gene therapy	enable high-dose chemotherapy with reduced side effects	Phase I
MDX-447 bispecific antibody	Medarex Annandale, NJ	MAb	head and neck, renal cancers	Phase I/II
MDX-H210 bispecific antibody	Medarex Annandale, NJ	MAb	breast, colorectal, kidney, ovarian, prostate cancers	Phase I/II
Melacine® melanoma theraccine (therapeutic vaccine)	Ribi ImmunoChem Hamilton, MT	vaccine	stage IV melanoma with interferon alpha	Phase III completed
	Ribi ImmunoChem Hamilton, MT Southwest Oncology Group San Antonio, TX	vaccine	stage II melanoma in patients with no evidence of disease to prevent recurrence following surgery to remove primary disease	Phase III

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
myeloid progenitor inhibitory factor-1	Human Genome Sciences Rockville, MD	interleukin	chemoprotection	Phase I
myelona-derived idiotypic antigen vaccine	National Cancer Institute Bethesda, MD	vaccine	multiple myeloma	Phase I NCI Trial

NEUPOGEN® Filgrastim (rG-CSF)	Amgen Thousand Oaks, CA	colony stimulation factor	acute myelogenouse leukemia (see also AIDS/HIV, respiratory)	application submitted
Omcaspar® PEG-L-asparaginase	Enzon Piscataway, NJ Phone-Poulenc Rorer Titusville, NJ		first-line treatment of acute lymphoblastic leukemia (ALL) adult ALL non-Hodgkin's lymphoma, chronic lymphocytic leukemia	in clinical trials
Oncolym®	Techniclone Tustin, CA	MAb	malignant glioma	Phase I
OncoRad® PR CYT-356-Y-90	CYTOGEN Princeton, NJ	MAb	targeted radiotherapy for prostate malignancies	Phase II
OncoScint® CR/OV satumomab pendetide	CYTOGEN Princeton, NJ	MAb	detection, staging and follow-up of breast cancer	Phase II
ONYX-015	Onyx Pharmaceuticals Richmond, CA	oncolytic virus therapy	p53 deficient cancers	Phase I/II
p53 and RAS vaccine	National Cancer Institute Bethesda, MD	vaccine	solid tumores	Phase I NCI Trial
p53 tumor suppressor gene	Schering-Plough Madison, NJ	gene therapy	lung cancers	Phase II
			solid tumors that carry the p53 gene mutation or deletion	Phase I
Panorex® edrecolomab	Centocor Malvem, PA	MAb	adjuvant therapy for post-operative colorectal cancer	Phase III
peripheral blood lymphocytes transduced with a gene encoding a chimeric T-cell receptor	National Cancer institute Bethesda, MD	gene therapy	ovarian cancer	Phase I NCI Trial
Proleukin® aldesleukin (interleukin-2)	Chiron Emeryville, CA	interleukin	acute myelogenous leukemia, non-Hodgkin's lymphoma (see also AIDS/HIV)	Phase II/III
promegapoletin	Searle Skokie, IL	growth factor	adjunctive hematopoietic therapy following chemotherapy	Phase I
Prostrac recombinant vaccinia virus	Therion Biologics Cambridge, MA	vaccine	prostate cancer	Phase I/II

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
RAS 5-17 peptide vaccine	National Cancer Institute Bethesda, MD	vaccine	solid tumores	Phase I NCI Trial
rCEA Vaccine recombinant carcinoembryonic antigen	Protein Sciences Meriden, CT	vaccine	breast, colon cacers	Phase I
Rebit® recombinant interferon beta-1a	Serono Laboratories Norwell, MA	interferon	colorectal cancers (see also infectious diseases, neurologic)	Phase III
			non-small-cell lung cancer	Phase I/II
recombinant human interleukin-12 (rhiL-12)	Genetics institute Cambridge, MA Wyeth-Ayerst Laboratories Philadelphia, PA	interleukin	cancer (see also infectious diseases)	Phase I/II
retroviral cevtor with tumor necrosis factor gene	Chiron Emeryville, CA	gene therapy	melanoma	Phase I
rF-gp 100 (recombinant fowlpox virus)	Therion Biologics Cambridge, MA	vaccine	melanoma	Phase I
rF-MART-1 (recombinant fowlpox virus)	Therion Biologics Cambridge, MA	vaccine	melanoma	Phase I
RIGScan® CR49 125 1-cc49 MAb	Neoprobe Dublin, OH	MAb	colorectal cancer	application submitted
Rituxan® rituximab	National Cancer Institute Bethesda, MD IDEC Pharmaceuticals San Diego, CA	MAb	leukemia, lymphoma	Phase II NCI Trial
Roferon®-A interferon alfa-2a, recombinant	Hoffmann-La Roche Nutley, NJ	interferon	malignant melanoma adjuvant	Phase III
rV-gp100 (recombinant vaccinia virus)	Therion Biologics Cambridge, MA	vaccine	melanoma	Phase I
rV-MART-1	Therion Biologics Cambridge, MA	vaccine	melanoma	Phase I
Serosilm™ somatropin (rDNA origin) for injection	Serono Laboratories Norwell, MA	human growth hormone	cancer cachexia (see also other)	Phase I/II
Sigosix® recombinant	Ares-Serono and Serono Laboratories	interleukin	hematological conditions	Phase I/II

interleukin-6 (r-IL-6)	Norwell, MA		(myelodysplastic syndromes, cancer)	

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
SMART™ M195 Hun 195	Protein Design Labs Mountain View, CA	MAb	acute myeloid leukemia	Phase II/III
			acute promyelocytic leukemia	Phase II
			advaced myeloid leukemia (with Bismuth-213)	Phase I
stem cell factor	Amgen Tousand Oaks, CA	stern cell factor	adjunct to chemotherapy	application submitted
SU101	SUGEN Redwood City, CA	PDGF-receptor tyrosine kinase inhibitor	malignant glioma	Phase III
			prostate cancer	Phase II
			solid tumors	Phase I/II
SU5416	SUGEN Redwood City, CA	angiogenesis inhibitor	solid tumors	Phase I
TBC CEA (vaccinia virus expressing carcinoembryonic antigen)	Therion Biologics Cambridge, MA	vaccine	colorectal and lung cancers	Phase I/II
Tcell-HDM	Coulter Cellular Therapies Boston, MA	cellular therapy	cancer	Phase I/II
Theratope® synthetic carbohydrate therapeutic vaccine	Biomira Edmonton, Alberta Chiron Emeryville, CA	vaccine	breast cancer	Phase II completed
thrombopoietin	Genetech S. San Francisco, CA	erythropoietin	thrombocytopenia related to cancer treatment	Phase II
Thyrogen® recombinant human thyroid-stimulating hormone	Genzyme Cambridge, MA		detection and treatment of thyroid cancer metastases	application submitted
TNT	Techniclone Tustin, CA	MAb	non-Hodgkin's B-cell lymphoma	Phase II/III
			solid tumors	Phase I
TriAB™ anti-idiotype antibody vaccine	Titan Pharmaceuticals S. San Francisco, CA	vaccine	breast cancer	Phase II

TriGem™ anti-idiotype antibody vaccine	Titan Pharmaceuticals S. San Francisco, CA	vaccine	small-cell lung cancer, melanoma	Phase I
urate oxidase (recombinantly-produced enzyme)	Sanoli New York, NY	recombinant enzyme	prophylaxis for chemotherapy-related hyperuricemia, treatment of cancer-related hyperuricemia	Phase III

CANCER AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
vaccinia-CEA 180KD vaccine	National Cancer Institute Bethesda, MD Therion Biologics Cabridge, MA	vaccine	advaced colorectal cancer	Phase I NCI Trial
Vaxid anti-idiotype DNA vaccine	Vical San Diego, CA	vaccine	B-cell and mantle cell lymphomas	Phase I
Xerecept™ human corticorropin-releasing factor (hCRF)	Neurobiological Technologies Richmond, CA		brain tumor edema	Phase II
Zenapax® daclizumab	Hoffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	certain blood cancers (see also eye, neurologic skin, transplantation)	Phase II

DIABETES AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
Beta Kine transforming growth factor-beta 2	Genzyme Tissue Repair Cambridge, MA	growth factor	chronic diabetic foot ulcers	Phase II
BetaRx-H encapsulated human islets	VivoRx Santa Monica, CA	cellular therapy	insulin-dependent diabetes	Phase I
BetaRx-P encapsulated porcine islets	VivoRx Santa Monica, CA	cellular therapy	insulin-dependent diabetes	Phase I

BetaRx-Pr encapsulated proliferated human islets	VivoRx Santa Monica, CA	cellular therapy	insulin-dependent diabetes	Phase I
Glucagen ™ recombinant human glucagon (protein)	Novo Nordisk Pharmacceuticals Princeton, NJ	recombinant human protein	hypoglycemia (see also digestive)	Phase III
glucagon for injection (rDNA origin)	Eli Lilly Indianapolis, IN	recombinant human protein	to treat severe hypoglycemic events in patients with diabetes and to aid in gastrointestinal diagnostic procedures	application submitted
insulinotropin	Soios Mountain View, CA		type 2 diabetes	Phase II
memantine	Neurobiological Technologies Richmond, CA		painful diabetic neuropathy (see also AIDS/HIV)	Phase II
nerve growth factor	Genentech S. San Francisco, CA	growth factor	diabetic peripheral neuropathy	Phase II

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DIABETES AND RELATED CONDITIONS

Product Name	Company	Product Category	Indication	Development Status
pimagedine	Alteon Ramsey, NJ Genentech S. San Francisco, CA		diabetic progressive kidney disease, diabetic end-stage kidney disease (see also neurologic)	Phase III
pramlintide	Amylin Pharmaceuticals San Diego, CA	human amylin analog	improved metabolic control, which includes glucose, weight and lipid profiles in type 1 and insulin-using type 2 diabetes	Phase III
rDNA insulin	Inhale Therapeutic System Palo Alto, CA	recombinant insulin	diabetes	Phase II
Trovert™	Sensus Austin, TX	human growth hormone	diabetes-related illnesses (see also growth disorders)	Phase II

DIGESTIVE DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Avakine™ chimeric anti-TNF antibody	Centocor Malvern, PA	MAb	Crohn's disease (see also autoimmune)	application submitted
Gastrimmune™ neutralizing G17 hormone	Aphron Woodland, CA	vaccine	gastroesophageal reflux disease, peptic and nonsterioidal anti-inflammatory drug ulcers (see also cancer)	Phase I/II
Glucagen™ recombinant human glucagon (protein)	Novo Nordisk Pharmaceuticals Princeton, NJ	recombinant human protein	gastrointestinal motility inhibition (see also diabetes)	Phase III
interleukin-10 (Il-10)	Schering-Plough Madison, NJ	interleukin	Crohn's disease, ulcerative colitis (see also AIDS/HIV autoimmune, heart, neurologic, respiratory, skin)	Phase II
ISIS 2302	Isis Phamaceuticals Carlsbad, CA	antisense	Crohn's disease, ulcerative colitis (see also autoimmune, skin, transplantation)	Phase II
LOP-02	Genentech S. San Francisco, CA LeukoSite Cambridge, MA	MAb	inflammatory bowel disease	Phase II
LeukoScan® sulesomab	Immunomedics Morris Plains, NJ	MAb	inflammatory bowel disease (see also infectious diseases)	Phase II
Neumega® recombinant human interleukin-11	Genetics Institute Cambridge, MA	interleukin	Crohn's Disease	Phase II
recombinant platelet activating factor-acetylhydrolase (rPAF-AH)	ICOS Bothell, WA		pancreatitis (see also respiratory)	Phase II

EYE CONDITIONS

Product Name	Company	Pr duct Category	Indication	Development Status
BPD-MA verteporfin	QLT Photo Therapeutics Vancouver, British Columbia		age-related macular degeneration	Phase III
MDX-RA immunotoxin	Medarex Annandale, NJ	MAb	prevention of secondary cataract	Phase III
Zenapax® daclizumab	Huffmann-La Roche Nutley, NJ Protein Design Labs Mountain View, CA	MAb	uveitis (see also cancer, neurologic, skin, transplantation)	Phase I/II

GENETIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
AAV CFTR gene therapy	Targeted Genetics Seattle, WA	gene therapy	cystic fibrosis (see also respiratory)	Phase I
CFTR/adenovirus vector	Genzyme Cambridge, MA	gene therapy	cystic fibrosis	Phase I
CFTR/lipid vector	Genzyme Cambridge, MA	gene therapy	cystic fibrosis	Phase I
ex vivo stem cells/ retrovirus vector	Genzyme Cambridge, MA	gene therapy	cystic fibrosis	Phase I
GR2134B7B	Glaxo Wellcome Rsch. Triangle Park, NC Megabios Burlingarne, CA	gene therapy	cystic fibrosis	Phase I/II
GV-10	Gen Vec Rockville, MD	gene therapy	cystic fibrosis	Phase I
HP-3	Milkhaus Laboratory Boxford, MA	signaling	cystic fibrosis	Phase II
Neuprex™ recombinant human bactericidal/permeability-increasing protein (rPBI-21)	XOMA Berkeley, CA	recombinant human protein	cystic fibrosis	Phase I
Pulmozyme® domas alpha, recombinant	Genentech S. San Francisco, CA	recombinant Dnas	early intervention in cystic fibrosis	Phase III
x-galachosidase A	Transkaryotic Therapies Cambridge, MA	enzyme	fabry's disease	Phase I

GROWTH DISORDERS

Product Name	Company	Product Category	Indication	Development Status
pralomerlin (GPA-748)	Wyeth-Ayerst Laboratories Philadelphia, PA	human growth hormone	adult growth hormone deficiency	Phase I
ProLease® hGH	Alkermes Cambridge, MA Genentech S. San Francisco, CA	human growth hormone	growth hormone deficiency in children	Phase III
Saizen® somatropin (rDNA origin for injection)	Serono Laboratories Norwell, MA	human growth hormone	management of adults with growth hormone disorder, intrauterine growth retardation in children (see also other)	Phase III
Trovert™	Sensus Austin, TX	human growth hormone	acromegaly (see also diabetes)	Phase II

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
AcuTect™ Tc-99m apcitide	Diatide Londonderry, NH	peptide	detection of carotid thrombus	Phase II
anti-CD-18 humanized MAb	Genentech S. San Francisco, CA	MAb	acute myocardial infarction	Phase II
BioByPass™ therapeutic angiogenesis (VEGF)	GenVec Rockville, MD	gene therapy	cardiovascular disease, including cardiac artery disease and peripheral vascular disease, either as an adjunct or alternative to existing surgical approaches such as cardiac artery bypass grafts and angioplasty	Phase I
Biostent™	NeoRx Seattle, WA		reduction of restinosis (vascular remodeling)following ballon angiolasty)	Phase I
Capiscint	Centocor Malvern, PA	MAb	atherosclerotic plaque imaging agent	Phase I

Corsevin™ M 12D10-Fab	Centocor Malvern, PA Corvas San Diego, CA	MAb	thrombolytic complications of percutaneous transluminal coronary angloplasty, coronary arterial starts, disseminates intravascular coagulation	Phase I
CPC-111	Cypros Phamaceuticals Carlsbad, CA	cellular therapy	coronary bypass surgery (see also blood)	Phase II
factor Vila inhibitors	Corvas San Diego, CA		deep vein thrombosis, pulmonary embolism, unstable angina, myocardial infarction	Phase I
FIBLAST® trafermin	Scios Mountain View, CA Wyeth-Ayerst Laboratories Philadelphia, PA	growth factor	peripheral vascular disease, coronary anery disease (see also neurologic)	Phase II

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
gene therapy	Collateral Therapeutics San Diego, CA	gene therapy	stable exertional argina	Phase I/II
growth factor	Chiron Emeryville, CA	growth factor	coronary artery disease	Phase I
h5G1.1-SCFV (recombinant)	Alexion Pharmaceuticals New Haven, CT Enzon Piscataway, NJ		cardiopulmonary bypass-associated inflammation using SCD® technology	Phase II
Hu23F2G MAb	ICOS Bothell, WA	MAb	myocardial infarction (see also neurologic, other)	Phase II
Intergrilin™ eptifibatide (IIb/IIIa platelet aggregation inhibitor)	COR Therapeutics S. San Francisco, CA Schering-Plough Madison, NJ		percutaneous transluminal coronary angioplasty, unstable angina	application submitted
			acute myocardial infarction	Phase II
interleukin-10 (IL-10)	Schering-Plough Madison, NJ	interleukin	ischemic reperfusion injury (see also AIDS/HIV, autoimmune, digestive, neurologic, respiratory, skin)	Phase I

lanoteplase	Bristol-Myers Squibb Princeton, NJ	t-PA	acute myocardial infarction	Phase III
LR-3280	Inex Pharmaceuticals Vancouver, BC Schwarz Pharma Milwaukee, WI	antisense	cardiovascular restinosis	Phase II
MH1-Fab imaging agent	American Biogenetic Sciences Boston, MA	MAb	in vivo imaging agent for the detection of cardiovascular thrombosis	Phase I/II
MPL®-C immunomodulator	Ribi ImmunoChem Hamilton, MT		prevention/amelioration of cardiac ischemia reperfusion injury	Phase II
Natrucor® BNP	Scios Mountain View, CA		acute congestive heart failure	Phase III completed/ application submitted
			cardiovascular pulmonary surgery	Phase I
Novastan® argatroban	Texas Biotechnology Houston, TX		heparin-induced thrombocytopenia thrombosis syndrome	application submitted
ReoPro® abciximab	Centocor Malvern, PA Eli Lilly Indianapolis, In	MAb	unstable angina (see also neurologic)	Phase III
			acute myocardial infarction	Phase II
rhAntithromnin III (recombinant)	Genzyme Cambridge, MA		control of blood clotting during coronary artery bypass surgery	Phase II completed
TNK (second-generation t-PA)	Genentech S. San Francisco, CA	t-PA	acute myocardial infarction	Phase III

HEART DISEASE

Product Name	Company	Product Category	Indication	Development Status
TP10	T Cell Sciences Needham, MA	recombinant soluble receptor	heart attack (see also respiratory, transplantation)	Phase I
VEGF	Genentech S. San Francisco, CA	growth factor	coronary artery disease	Phase I

VEGF 121 (vascular endothelial growth factor)	Scios Mountain View, CA	growth factor	cardiovascular disorders	Phase I
Xubix™ sibratiban oral IIb/IIIa antagonist	Genentech S. San Francisco, CA		acute coronary syndrome	Phase III

INFECTIOUS DISEASE

Product Name	Company	Product Category	Indication	Development Status
adefovir dipivoxil	Gilead Sciences Foster City, CA	nucleotide analogue	hepatitis B	Phase II
Alferon N Gel® interferon alfa0n3	Interferon Sciences New Brunswick, NJ	interferon	human papillomavirus infections	Phase II
Alferon N Injection® interferon alfa-n3	Interferon Sciences New Brunswick, NJ	interferon	chronic hepatitis C infections (see also AIDS/HIV)	Phase III
			genital warts	Phase II
Ampligen®	Hemispherx Biopharma	interferon	hepatitis (see also AIDS/HIV, cancer, other)	Phase I/II
anti-tumor necrosis factor MAb	Chiron Emeryville, CA	MAb	sepsis	Phase II/III
Campylobacter vaccine	Antex Biopharma New York, NY	cellular vaccine	traveler's diarrhea (Campylobacter infections)	Phase II
CMV vaccine	Chiron Emeryville, CA	vaccine	cytomegalovirus infection	Phase II
DTaP vaccine	Chiron Emeryville, CA	vaccine	diphtheria, tetanus, acellular pertussis	Phase III
Epstein-Barr virus vaccine	Aviron Mountain View, CA SmithKline Beecham Philadelphia, PA	recombinant subunit vaccine	prevention of Epstein-Barr virus infection (cause of mononucleosis infection)	Phase I
genital herpes vaccine	Glaxo Wellcome Rsch. Triangle Park, NC	vaccine	genital herpes	Phase I
Helicobacter vaccine	Antex Biologics Gaithersburg, MD	cellular vaccine	peptic ulcers (Helicobacter pylori infections)	Phase I

INFECTIOUS DISEASE

Product Name	Company	Product Category	Indication	Development Status
hepatitis A vaccine	Chiron Emeryville, CA	vaccine	hepatitis A	Phase III
hepatitis B DNA vaccine	Powderject Vaccines Madison, WI	DNA vaccine	hepatitis B prevention	Phase I
hepatitis B vaccine (recombinant)	SmithKline Beecham Philadelphia, PA	vaccine	treatment of hepatitis B	Phase II
herpes simplex vaccine (recombinant)	SmithKline Beecham Philadelphia, PA	vaccine	prevention of herpes simplex infection	Phase III
HPV vaccine	Medimmune Gaithersburg, MD SmithKline Beecham Philadelphia, PA	vaccine	genital warts (see also cancer)	Phase I
human anti-hepatitis B antibody (OST 577)	Protein Design Labs Mountain View, CA	MAb	liver transplantation due to chronic hepatitis B infection	Phase I/II completed
Intron®A interferon alfa-2b (recombinant)	Schering-Plough Madison, NJ	interferon	pediatric hepatitis B, self-injectable dosing system for hepatitis C (see also cancer)	application submitted
			hepatitis C (PEG-intron A)	Phase III
Intron®A/ Rebeiol™ interferon alfa-2b (recombinant)/ribavirin	Schering-Plough Madison, NJ	interferon	relapsed hepatitis C	application submitted
			naive hepatitis C (not previously treated with interferon)	Phase III
			hepatitis C (PEG-intron A/Rebetol)	Phase I
LeukoScan® sulesomab	Immunomedics Morris Plains, NJ	MAb	diagnosis of osteomyelitis, infected prosthesis, appendicitis (see also digestive)	application submitted
Lyme borreliosis protein vaccine	Pasteur Merieux Connaught Swiftwater, PA	vaccine	Lyme disease	Phase III
Lyme disease vaccine (recombinant)	SmithKline Beecham Philadelphia, PA	vaccine	prevention of Lyme disease	application submitted
MAK 195F	Knoll Pharmaceutical Mt. Olive, NJ	MAb	sepsis	Phase III
MEDI-491 parvovirus B 19 vaccine	Medimmune Gaithersburg, MD	vaccine	B 19 parvovirus-induced miscarriages and anemia	Phase I

meningococcus C vaccine	Chiron Emeryville, CA	vaccine	meningococcus C	Phase II

INFECTIOUS DISEASE

Product Name	Company	Product Category	Indication	Development Status
MPL® immunomodulator (25+ antigens for adult and pediatric applications)	Ribi ImmunoChem Hamilton, MT	vaccine	infectious diseases (see also AIDS/HIV)	in clinical trials
Neuprex™ recombinant human bactericidal/permeability-increasing protein (rBPI-21)	XOMA Berkeley, CA	recombinant human protein	meningococcemia (see also genetic, other)	Phase III
			antibiotic adjuvant in intra-abdominal infections	Phase II
Protovir™ human anti-CMV antibody	Protein Design Labs Mountain View, CA	MAb	cytomegalovirus infections in bone marrow transplant patients	Phase II completed
Rebir® recombinant interferon beta-1a	Serono Laboratories Norwell, MA	interferon	viral infections (see also cancer, neurologic)	Phase II/III
recombinant human activated protein C (rhAPC)	Eli Lilly Indianapolis, IN	recombinant human protein	treatment of severe sepsis	Phase II
recombinant human interleukin-12 (rhiL-12)	Genetics Institute Cambridge, MA Wyeth-Ayerst Laboratories Philadelphia, PA	interleukin	infectious diseases (see also cancer)	Phase I/II
Rotashield™ rotavirus vaccine, live, oral, tetravalent	Wyeth-Lederle Vaccines & Pediatrics Philadelphia, PA	continuous cell line vaccine	prevention of rotaviral gastroenteritis in infants	application submitted
rotavirus vaccine	Virus Research Institute Cambridge, MA	vaccine	rotavirus in infants	Phase II
Savvy™ C31G	Biosyn Philadelphia, PA	microbicide	infectious disease	Phase I
Tenefuse® lenercept (TNF-receptor fusion protein)	Hoffmann-La Roche Nutley, NJ	recombinant soluble receptor	septic shock, severe sepsis	Phase III
tifacogin	Chiron Emeryville, CA Searle Skokie, IL	tissue factor pathway inhibitor	sepsis	Phase II

INFERTILITY

Product Name	Company	Product Category	Indication	Development Status
Antide™ gonadotropin hormone-releasing hormone antagonist (GhRHA)	Ares/Serono and Serono Laboratories Norwell, MA	hormone-releasing hormone antagonist	female infertility	Phase I
Gonal-P® recombinant human follicle-stimulation hormone (r-FSH)	Serono Laboratories Norwell, MA	recombinant fertility hormone	male infertility	Phase III
LhADI® recombinant human leutinizing hormone (r-hLH)	Ares/Serono and Serono Laboratories Norwell, MA	recombinant fertility hormone	female infertility-follicular support, stimulation of follicular development	Phase II/III
Ovidrel® recombinant human chorionic gonadotropin (r-hCG)	Ares/Serono and Serono Laboratories Norwell, MA	recombinant gonadotropin	female infertility (see also AIDS/HIV)	Phase III

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
Activase® alteplase, recombinant	Genentech S. San Francisco, CA	t-PA	acute ischemic stroke within 3 to 5 hours of symptom onset	Phase III
AnergiX™ MS	Anergen Redwood City, CA	functional antigenics immuno-therapy	multiple sclerosis	Phase I
Antergren natalizumab	Athena Neurosciences S. San Francisco, CA	MAb	multiple sclerosis flames	Phase II
ATM027 humanized MAb	T Cell Sciences Needham, MA	MAb	multiple sclerosis	Phase I
Avonex® interferon beta-Ta	Biogen Cambridge, MA	interferon	secondary, progressive multiple sclerosis (see also cancer)	Phase III
Betaseron® recombinant interferon beta-1b	Berlex Laboratories Wayne, NJ Chiron Emeryville, CA	interferon	chronic progressive multiple sclerosis (see also cancer)	Phase III

brain-derived neurotrophic factor (BDNF)	Amegen Thousand Oaks, CA Regeneron Pharmaceuticals Tarrytown, NY	growth factor	amyotrophic lateral sclerosis	Phase I

NEUROLOGIC DISORDERS

Product Name	Company	Product Category	Indication	Development Status
CPC-211	Cypros Pharmaceuticals Carlsbad, CA	cellular therapy	ischemic stroke, traumatic brain injury	Phase II
enlimomab (anti0ICAN-1 MAb)	Boehringer Ingelheim Pharmaceuticals Ridgefield, CT	MAb	stroke (see also other)	Phase II/III
FIBLAST® tragermin	Scios Mountain View, CA Wyeth-Ayerst Laboratories Philadelphia, PA	growth factor	stroke (see also heart)	Phase II/III
Hu23F2G MAb	ICOS Bothell, WA	MAb	multiple sclerosis, ischemic stroke (see also heart, other)	Phase II
interleukin-10 (iL-10)	Schering-Plough Madison, NJ	interleukin	multiple sclerosis (see also AIDS/HIV, autoimmune, digestive, heart, respiratory, skin)	Phase I
IR 208 therapeutic vaccine	Immune Response Corp. Carlsbad, CA	vaccine	multiple sclerosis	Phase I
LDP-01	LeukoSite Cambridge, MA	MAb	stroke (see also transplantation)	Phase I/II
MS-TCR	Connectics Pal Alto, CA	vaccine	multiple sclerosis	Phase I/II
Myotrophin® rhIGF-1	Cephalon West Chester, PA Chiron Emeryville, CA	growth factor	amyotrophic lateral sclerosis	application submitted
			peripheral neuropathies	Phase II
NeuroCell™-FE (cellular transplantation therapy)	Diacrin Charlestown, MA	cellular therapy	focal epilepsy	Phase I
NeuroCell™-HD (cellular transplantation therapy)	Diacrin Charlestown, MA Genzyme Tissue Repair Cambridge, MA	cellular therapy	Huntington's disease	Phase I completed